BMJ Open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005922
Article Type:	Research
Date Submitted by the Author:	17-Jun-2014
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\Primary Subject Heading\:	Health economics
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Cost-Benefit Analysis, Diagnostic Techniques, Obstetrical and Gynecological, Down Syndrome, Prenatal diagnosis < OBSTETRICS

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Introducing the non-invasive prenatal test for trisomy 21 in Belgium: a cost-consequences analysis

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Abstract

Background: First and second trimester screening for trisomy 21 (T21) is reimbursed for all pregnant women in Belgium. Using a cut-off risk of 1:300 for T21, about 5% of all pregnant women are referred for definitive prenatal diagnosis using an invasive test, at a sensitivity of (only) 72.5%. Sensitivity and specificity of the non-invasive prenatal test (NIPT) are over 99% but comes at a cost of €460 (£373) per test. The objective is to estimate the consequences of introducing NIPT for the detection of T21.

Methods: A cost-consequences analysis was performed presenting the impact on benefits, harms and costs. Context-specific real-world information was available to set up a model reflecting the current screening situation in Belgium. This model was used to construct the 2nd and 1st line NIPT screening scenarios applying information from the literature on NIPT's test accuracy.

Results: Introducing NIPT in 1st and 2nd line reduces harms by decreasing the number of procedure-related miscarriages after invasive testing. Offering NIPT in 1st line additionally will miss fewer cases of T21 due to less false negative test results. The introduction of NIPT in 2nd line results in cost savings which is not true for NIPT at current price in 1st line. If NIPT is offered to all pregnant women, the price should be lowered to about €150 to keep the screening cost per T21 diagnosis constant.

Conclusions: In Belgium, introduction and reimbursement of NIPT as 2nd line triage test significantly reduces procedure-related miscarriages without increasing short-term screening costs. Offering and reimbursing NIPT in 1st line to all pregnant women is preferred on the long term, as it would in addition miss fewer cases of T21. However, taking into account the governmental limited resources for universal reimbursement, the price of NIPT should first be lowered substantially before this can be realized.

Strengths and limitations of this study

- The major strength of the model is the availability of context-specific real-world information and the ability to reflect the current Belgian screening situation by calibrating the model to the number of women screened, the expected and observed number of children born with Down syndrome and the number of invasive tests performed in Belgium. This calibration assures that the initial screening model reflects the current Belgian screening situation as good as possible.

- The most important limitation of our analysis is, due to a lack of reliable data, the inability to apply a long-term horizon and translate outcomes to incremental cost-effectiveness ratios expressing results in euros per (quality-adjusted) life-year gained. However, by presenting the consequences of screening in a transparent way (which includes both the detection of T21, the number of Down births whether or not after a false negative screening test, and the number of procedure-related losses), we try to inform the policy makers in a transparent way about the possible consequences of introducing NIPT in different settings.

- In order to avoid a "black box" and to provide other researchers the possibility to use and adopt the model to their context, details of the full model are included in supplementary files with a step by step explanation for every transition.

Introduction

Prenatal diagnosis of Down syndrome allows for informed decision making with regard to pregnancy continuation or termination. Multiple prenatal trisomy 21 (T21, Down syndrome)/aneuploidy screening strategies in the first and second trimester have been developed.[1] The most commonly used approach for first trimester screening in Belgium is the combination of the nuchal translucency (NT) ultrasound measure at week 12 (week 11-14), the level of free-beta-hCG (human chorionic gonadotrophin hormone) and PAPP-A (pregnancy associated plasma protein-A), in combination with age and medical history. The T21 screening in Belgium is fully reimbursed for all pregnant women and has a high uptake of nearly 80%. However, the overall sensitivity is rather low (~72.5%) compared with reports from neighbouring countries. This moderate performance is likely related to the absence of an obligatory quality assurance system for the nuchal translucency assessment in Belgium.

The non-invasive prenatal testing (NIPT) is performed on a blood sample of the pregnant woman containing circulating cell free DNA both from the mother and the placenta, which in nearly all cases is representative for the foetal DNA. NIPT has been shown to be highly accurate in the detection of common fetal autosomal trisomies, especially T21.[1] However, about 4% of the tests will not provide a result (reduced by half after repeated sampling). The 'no result' NIPT is often caused by a low proportion of fetal DNA, as seen when the sample is obtained before gestational week 12 or in obese women. In dizygotic twin pregnancies NIPT also remains a challenge. Because of its high cost NIPT was originally positioned as triage test in pregnancies referred for invasive testing (chorionic villus sampling (CVS) or amnioscentesis) because of a calculated risk, e.g. above 1:300. NIPT for primary screening (at week 12) of pregnant women with a NT under 3.5mm is becoming a real possibility in view of the growing number of validation studies in low risk pregnancies[2] and especially the prospect of a lower cost per test.

As part of its government-approved work programme, the Belgian healthcare knowledge centre (KCE) performed an economic evaluation of introducing NIPT in prenatal diagnosis of Down syndrome. The research questions were the following: 1) What is the impact of introducing NIPT on the benefits and harms of screening for trisomy 21 in the Belgian context? Benefits can be expressed in terms of detection of trisomy 21 such that informed decision making is possible. Possible harms in the process include membrane rupture with amniotic fluid leakage or miscarriage after an invasive test, and the risk of missing the detection of Down syndrome because of a false negative test result. 2) What is the impact on costs and budget for the health insurance of introducing NIPT? What is the cost for the detection of a case of trisomy 21 after introducing NIPT?

Methods

A time-dependent multi-stage transition probability model was developed in Excel in order to assess the consequences of introducing NIPT. This model allows following pregnant women during the screening process and pregnancy up to birth, taking in to account e.g. spontaneous miscarriage rates. In accordance with the Belgian guidelines for economic evaluations,[3] the analysis includes direct health care costs from the perspective of the health care payer. Payments out of the public healthcare budget as well as patients' co-payments are included.

A short-term time horizon was applied in which costs and effects before birth were considered. Due to this short-term horizon, no discount rate was applied. A long term-horizon translating results in extra costs per (quality-adjusted) life year ((QA)LY) gained was not modelled due to a lack of reliable data and thus the hypothetical character of this scenario. In this cost-consequences analysis, the following outcomes were calculated: total number of life births and number of children born with Down syndrome, cases of T21 diagnosed during pregnancy, children with Down syndrome born after a false-negative screening result, procedure-related miscarriages (related to T21 detection), short-term screening cost, short-term screening cost per case of T21 diagnosed, and incremental cost per extra case of T21 diagnosed.

Population

The model includes all pregnancies in the Belgian population, except for twin pregnancies. These represent 1.8% of pregnancies and correspond to about 2.1% of all T21 cases.[4][5] Complete and up to date data from Flanders, the northern community of Belgium representing 54% of the children born in Belgium, were extrapolated to the Belgian situation. The model takes into account the different probabilities of a spontaneous loss of the fetus, for T21 and non-T21 pregnancies, adjusted for gestational week (e.g. 5% and 36% at week 10 for all and T21-pregnancies, respectively (see Table 1)).[6,7] A total of 122 739 births in Belgium in 2012 thus corresponds to 129 199 singleton pregnancies at gestational week 10. The observed life birth prevalence of Down syndrome in Belgium, extrapolated from the Flanders registry, was estimated at 98 in 2012, of which 96 after singleton pregnancies. Based on the age distribution of the pregnant women in Flanders and reported age related prevalence of Down syndrome,[8] 219 T21 singleton life births would be expected without screening, corresponding to 342 pregnancies at week 10. These numbers of expected and observed births of children with Down syndrome were used to calibrate the model.[9]

Comparators

The current practice in Belgium for first- and second trimester screening for T21 is modelled and serves as the initial comparator. NIPT is the intervention under consideration and is considered both as contingent test (i.e. as triage or 2nd line test) and for primary screening (i.e. as first-line test). Figure 1 presents the triage scenario in which NIPT is offered only to women at increased risk (>1:300) after current screening. The risk cut-off is changed in modelled scenario analyses (see further). The figures representing the current Belgian screening strategy and NIPT in 1st and 2nd line are presented as supplementary material.

Input variables

The values and probabilities of all input variables in the models are provided in Table 1. Costs for screening, adverse events and pregnancy termination are included and are expressed in € for the year 2013 (Table 2). These costs are based on data from our National Institute for Health and Disability Insurance (NIHDI).

Based on reimbursement data from NIHDI for the year 2011, excluding the 1.8% twin pregnancies, 78 168 pregnant women participate in first trimester screening (€80.42 per activity) and another 21 451 in second trimester screening (€45.03 per activity). After adjustments for gestational week, the total screening uptake is estimated at 78.87%. If we also assume 1000 women that immediately undergo invasive testing for T21, the overall uptake of any type of testing for Down syndrome increases to 79.74%. In the reference case, this screening uptake is kept constant.

Sensitivity and specificity of screening at different risk cut-offs are based on the receiver operator characteristics (ROC) curve data from AML (Algemeen Medisch Laboratorium bvba), a large laboratory covering 40% of the first and second trimester screenings for Down syndrome in Flanders. In the reference case, a risk cut-off level of 1:300 is applied, which results in a sensitivity of 72.54% (95%CI: 0.649 – 0.795) and specificity of 95.03% (95%CI: 0.949 – 0.952). This is varied in modelled scenario analyses (see further).

The baseline cost for NIPT (and also for a repeat NIPT if needed) is set at €460, i.e. the current price charged by the university hospital of Leuven in Belgium. We assume a no first time NIPT result in 4% (3-7%) of cases, reduced to 2% (1-3%) after a repeat NIPT. These estimates are in agreement with 11 studies reviewed by Benn et al.[10] In the primary NIPT model we assume these 2% of women tested will accept to fall back on the current screening and not opt directly for an invasive test. Based on an overview of existing evidence, the sensitivity and specificity of NIPT tests with a result is assumed to be 99.3% (95%CI: 98.2-99.8%) and 99.84% (95%CI: 99.69-99.92%), respectively.[10] No additional cost for NIPT counselling is included since it is assumed that this would happen in a similar way as in the current screening approach and thus does not occur to be an incremental cost.

Invasive diagnostic testing is recommended after a positive current screening test or NIPT result in order to confirm the results. The proportion of women undergoing an invasive test after a positive screening was 86.9% (95%CI: 83.9 to 89.5%) in a large study in Paris.[11] We use a similar probability of 87.5% (80-95%) which was obtained after model calibration. Having no real-world data at our disposal, this proportion of women undergoing an invasive test is also used in the model after a positive or a 'no result' for NIPT in case of triage, or after a positive NIPT result in case of first line NIPT. In case of a 'no result' NIPT in first line we assume screening continues with the current approach. The total cost for an invasive procedure and genetic testing for Down syndrome is on average €934 based on the data of NIHDI.

The total number of invasive tests in Belgium in 2011 is 7586. Based on the modelling exercise, 4374 are performed following the current screening. Based on expert opinion and model calibration, the remaining tests are performed (1) following a NT>3.5mm (n=398), (2) for other indications (but samples are also tested for T21) (n=1814) and (3) in pregnant women who want more certainty without being at increased risk (n=1000). These 1000 women represent 0.8% of all pregnant women and we assume no prior screening test is performed or billed. The number of 1000 primary invasive tests is included in all modelled scenarios of current screening and triage NIPT. However, we assume these 1000 women will opt for primary NIPT screening once available as NIPT provides more certainty. In Belgium, the samples obtained from invasive procedures are analyzed at one of the eight centres for human genetics. The test sensitivity of chorionic villus sampling (CVS) has been found to be somewhat lower compared to amniocentesis (98.47% versus 99.32%, respectively).[12] However, in our model, we assume 100% accuracy for these last-stage analyses.

Invasive testing carries a risk of membrane rupture with amniotic fluid leakage.[13] This may lead in about 1% of procedures to a hospitalisation of about one week at a cost of €3515 and in about 1% to a procedure-related miscarriage. This miscarriage rate may be more frequent after CVS compared with amniocentesis, and may be less frequent in experienced hands.[14] It has been reported that 89% to 97% of the women who received a positive diagnosis of T21 during the prenatal period had an induced abortion.[15] Belgian data covering a 10 year period (2003-2012) in a single centre show a

diagnosis of T21 after an invasive test during pregnancy in 44 cases. The pregnancy was terminated in 42 out of these 44 cases (95.45%, 95%CI 87.7% – 99.4%), which is used in the model. This is in agreement with a proportion of 94.8% (95% CI 92.5–96.5) reported in Paris[11] and 93.3% (250 out of 268) in the UK.[16] Pregnancy termination is associated with a 24-48 hour hospitalization and costs on average €914.

Uncertainty and scenario analyses

Both one-way and probabilistic sensitivity analyses were applied. The impact of uncertainty around all the model's input parameters on the results was modelled probabilistically. The applied distribution depends on the type of variable:[17] probabilities (e.g. NIPT test failure or procedure related fetal loss) and test characteristics (sensitivity and specificity) were modelled as beta distributions. This distribution is limited to the 0-1 scale and reflects the possible outcomes for these variables. For cost variables with less informative data for a stochastic distribution, uniform distributions were applied.

Several one-way scenario analyses are modelled:

- The cut-off risk of 1:300 for T21 is changed to 1:600, 1:1100, 1:1700, 1:2400, and 1:3000.
- A scenario with 90% NIPT uptake in first line (instead of the current uptake with 1st and 2nd trimester screening of about 80%) is presented without changing any other input variable.
- A threshold analysis is performed changing the price of NIPT to keep the short-term costs per case of T21 diagnosed at the same level as in the current screening scenario.
- A scenario with improved performance of the current screening (sensitivity of 77.5% instead of 72.5%)

For further details, we refer to the supplementary file. 1000 Latin Hypercube simulations are performed and correlation coefficients are calculated in a probabilistic sensitivity analysis. The @Risk add-on tool (Palisade Corporation) is used for probabilistic modelling and sensitivity analyses.

Table 1 – Input variables (volumes and probabilities)

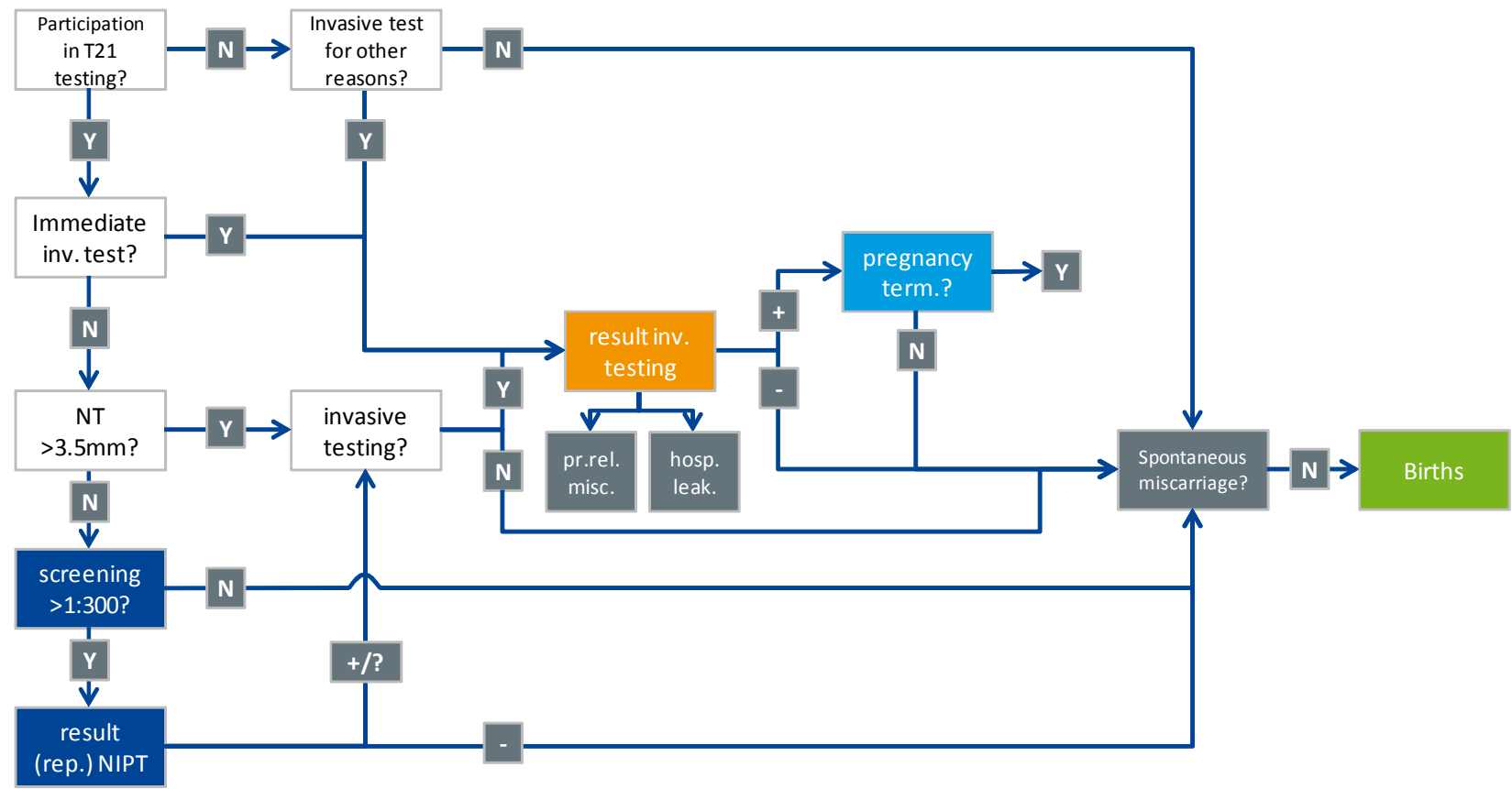| Variable	Mean	Uncertainty	Source
Screening uptake	78.87%	Scenario analysis: 90%	Belgian data
Testing uptake (i.e. screening + invasive test without prior screening)	79.74%		Belgian data
Current screening accuracy		Scenario analysis +	Belgian data
Sensitivity	72.54%	Beta(103;39)	
Specificity	95.03%	Beta(117 144;6121)	
NIPT			Literature[10]
Sensitivity	99.3%	95%CI: 98.2-99.8% (Beta(6;1.06);2.5%:0.982;97.5%:0.998)	
Specificity	99.84%	95%CI: 99.69-99.92% (Beta(3;1.014);2.5%:0.9969;97.5%:0.9992)	
NIPT test failure rate			Expert opinion plus literature[10]
First test (at week 12)	4%	Min.-max: 3-7% (Beta(2;6);min:0.03;max:0.07)	
Second test (at week 13)	2%	Min.-max: 1-3% (Beta(2;2);min:0.01;max:0.03)	
Probability of having an invasive test (after a positive screening test or NIPT)	87.5%	Min.-max: 0.8-0.95% (Beta(2;2);min:0,8;max:0,95)	Assumption and model fitting plus literature[11]
Number of invasive tests without prior screening	3212	Conditional Beta distribution (313.9; 1000; 84.1; 1814)	Belgian data and model fitting; literature[18]
Invasive testing (CVS or amniocentesis)		/	Considered as gold standard
Sensitivity	100%		
Specificity	100%		
Procedure related fetal loss after invasive test	1%	Min.-max: 0.5-2% (Beta(2;4);min:0.005;max:0.02)	Literature[14]
Hospitalization for amniotic fluid leakage after invasive test	1%	Min.-max: 0.5-2% (Beta(2;4);min:0.005;max:0.02)	Literature[13]
Pregnancy termination after T21 diagnosis	95.45%	Beta(42;2)	Belgian data and literature[11 16]
Spontaneous miscarriage			Literature[6,7]
Miscarriage all (p)		0.05, 0.025, 0.015 at week 10, 12, and 14, respectively.*	
T21 miscarriage (p)		0.36, 0.3, 0.25 at week 10, 12, and 14, respectively.	

*CVS: chorionic villus sampling; NIPT: non-invasive prenatal test. *Rounded numbers extracted from a published figure.[7]*

Table 2 – Input variables (costs)

Variable	Mean	Uncertainty	Source
1st trimester screening	€80.42	/	NIHDI
2nd trimester screening	€45.03	/	NIHDI
NIPT	€460	Scenario and threshold analysis	University Hospital Leuven
Invasive diagnostic test	€934.21	Min.-max: €887.71; €980.71 (uniform)	NIHDI (and expert opinion for the distribution)
Hospitalization for leakage	€3514.54	+/- 20% (uniform)	NIHDI (and expert opinion for the distribution)
Pregnancy termination	€914.39	Min.-max: €658.24; €1170.54 (uniform)	NIHDI (and expert opinion for the distribution)

NIHDI: National Institute for Health and Disability Insurance; NIPT: non-invasive prenatal test. Exchange rate May 22, 2014: €1 = £0.81.

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Figure 1 – Screening strategy with NIPT as triage test

Hosp.leak.: hospitalisation for leakage; inv.: invasive; pr.rel.misc.: procedure-related miscarriage; rep.: repeat; term.: termination.

Results

Reference case

Table 3 presents the results for the three reference case scenarios. In the current screening situation without NIPT, 170 cases of T21 are diagnosed. 96 children with Down syndrome are born, of whom 41 after a false negative screening result. There are 58 iatrogenic miscarriages after T21-related invasive testing. Total short-term costs of screening are almost €15 million and the short term average cost per T21 diagnosed is about €87 000.

Introducing NIPT as triage test (cut-off 1:300) results in one extra case of T21 diagnosis missed after a false negative NIPT result. However, there are much less procedure-related miscarriages after T21-related invasive testing (16 versus 58). Both total short term costs (minus €1.6mio) and short term average cost per case of T21 diagnosed are lower.

Introducing NIPT in 1st line results in more cases of T21 diagnosed (n=215 versus currently 170), very few children with Down syndrome born after a false negative screening result (n=2 versus 41 currently), a significant decrease in iatrogenic miscarriages related to T21 (n=8 versus 58 currently). However, at a price of NIPT of €460, the short term budget increases to almost €51 million with a tripled average cost per case of T21 diagnosed of about €236 000. The extra cost per extra case of T21 diagnosed versus NIPT as triage test is about €840 000.

Table 3 – Results

Test strategy	Current screening	NIPT 2nd line	NIPT 1st line
(Down) births, diagnosis and miscarriages			
N° of births	122543	122554	122560
N° of Down born	96	97	63
N° of Down born (false neg. screening)	41	42	2
N° of T21 detected	170	169	215
N° of proc.rel. miscarriages	76	34	26
N° of T21 proc.rel. misc.	58	16	8
Costs for testing during pregnancy			
1st & 2nd trim. screening cost	€7.252.215	€7.252.215	€89.123
NIPT cost	€0	€2.390.929	€47.969.932
Cost invasive tests	€7.086.886	€3.203.417	€2.435.450
Cost hosp.leakage & pregn.term.	€415.728	€268.375	€279.539
Total cost (Short term)	**€14.754.829**	**€13.114.935**	**€50.774.045**
Short term cost/T21 detected	**€86.944**	**€77.696**	**€236.436**
Extra cost per extra T21 detected	/	€2.738.197§	€839.936

Proc.rel. misc.: procedure-related miscarriage; § This result is located in the 3rd quadrant, i.e. fewer cases of T21 diagnosed with a lower cost. The results with their 95% credibility intervals (CrI) are not presented but are available upon request.
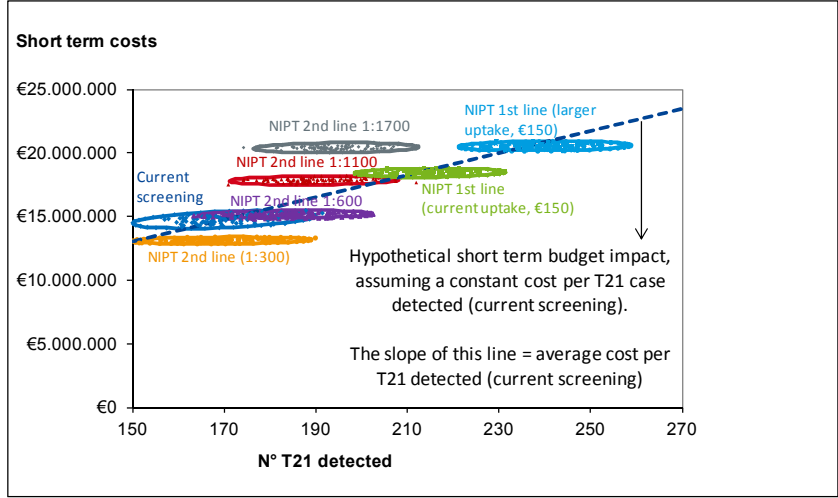
Uncertainty and scenario analyses

Figure 2 provides an overview of the most relevant scenarios, including the impact of uncertainty of all input variables. The x- and y-axis represent the number of T21 diagnoses and total short term costs, respectively. We remark that these are not the only outcomes of importance. Other outcomes,

such as the number of procedure-related miscarriages should also be taken into consideration. Further details on all outcomes are mentioned in supplementary tables.

More patients would receive NIPT in 2nd line if the risk cut-off after 1st and 2nd trimester screening is lowered. As a result, the number of T21 detections would increase and fewer children with Down syndrome would be born after a false negative screening. The number of procedure-related miscarriages would increase only slightly each time the cut-off risk is lowered. The short term total screening costs and average cost per T21 detected are lower compared with the current screening situation if NIPT is used as triage test with a risk cut-off of up to 1:600. However, if the risk-cut off is lowered further the extra cost per extra T21 detected increases exponentially (Figure 2 and Table 6 in supplementary material).

The threshold analysis resulted in a price of about €152 which would keep the short-term screening cost per T21 diagnosed constant if NIPT is used in first line. This is illustrated in Figure 2. At this price and the current screening uptake of about 80%, we would do much better (more T21 detected, less children born with Down syndrome after false negative screening and less procedure-related miscarriages). At a constant average cost of about €87000 per case of T21 diagnosed this would lead to an increase in the short term costs, proportional to the increased detection rate (see supplementary table). The same is shown in Figure 2 for a 90% uptake scenario.

Figure 2 – Presentation of most relevant screening scenarios

See the discussion for further explanation on the interpretation of the line presenting the 'average cost per T21 detected (current screening)'. Remark: This figure does not present other outcomes of importance, such as the number of procedure-related miscarriages.

The probabilistic sensitivity analysis showed that the most important stochastic variables in the current screening model and the model with NIPT in 2nd line are the sensitivity of current screening and the probability of having an invasive test after positive screening.

Discussion

In Belgium, almost 100 000 women participate in current screening. Introducing NIPT as contingent test or in 1st line is expected to reduce the number of procedure-related miscarriages. In addition, the number of T21 diagnoses missed by screening will be strongly reduced when NIPT is used in 1st

line. Whereas NIPT as a contingent test at a price of €460 will lead to short term savings of about €1.6 million, NIPT in 1st line has a high impact on budgets, unless the price of NIPT is considerably reduced.

Strengths and limitations of study

The major strength of the model is the availability of context-specific real-world information and the ability to reflect the current Belgian screening situation by calibrating the model to the number of women screened, the expected and observed number of children born with Down syndrome and the number of invasive tests performed in Belgium. This calibration assures that the initial screening model, including a large amount of real-world Belgian data on test characteristics, probabilities and costs, reflects the current Belgian screening situation as good as possible. This initial model is then used to construct the 2nd and 1st line NIPT screening situation. The expected 219 births with Down syndrome if no screening is performed is used as a control variable and checked in all models and all simulations. Full details of the models are available in supplementary material.

The major weakness of the model is the inability to apply a long-term horizon and translate outcomes to incremental cost-effectiveness ratios expressing results in euros per (quality-adjusted) life-year gained. Two studies incorporate a lifetime cost of Down syndrome from a societal perspective of $940 000[19] and $677 000,[20] respectively. A lifetime cost of Down syndrome of $900 000 is also mentioned by Cuckle et al.[21] This amount is extrapolated from a 1992 average lifetime societal costs for an individual with Down syndrome of $451 000.[22] The largest part (64%) was due to indirect costs (productivity losses) which were calculated with the human capital approach. However, in contrast to the friction cost approach, this overestimates the total incremental cost for society. The friction-cost method, which is recommended by the Belgian guidelines for economic evaluations,[3] is based on the idea that organizations need a certain time span (the friction period) to restore the initial production level after an employee becomes absent from work. The amount of production lost to society will be much lower than the above stated numbers and depends on the length of this friction period.

Furthermore, quality of life is of major importance. One study included maternal QALYs in their analysis.[19] The QoL data used in this study were based on studies of Kuppermann et al.[23-25] in women seeking genetic counselling and being less than 20 weeks pregnant. Their preferences, based on a hypothetical situation, might be very different from parents having a child with Down syndrome. Both the impact on life years (as a result of procedure-related or induced miscarriage) and QoL (e.g. on parents during testing, people with/without Down syndrome and their parents) are not clear enough to make proper calculations with a long-term horizon. Furthermore, as stated by Petrou,[26] "*the matter is complicated further when one considers the positive utility effects that might accrue from a future 'replacement' child. The important point to note, however, is that an objective economic evaluation that measures and values the resource savings that follow the abortion of the affected foetus or unborn child requires a commensurate measurement and valuation of averted benefits. Furthermore, this remains the case whenever averted costs are incorporated into the evaluation, since the foetus or unborn child is necessarily ascribed a future human status that, by any measure, will have positive value and utility.*" There are also other relevant costs outside the health care system. "*When the resource use implications for other sectors of society are considered the issue becomes more complicated: for example, the avoided excess costs associated with educational and institutional care, would need to be considered, as well as the costs of voluntary services and care*

incurred by the family."[27] Gathering the necessary information on all these incremental elements could be the subject of future research.

In an ideal situation, all of these incremental elements would be taken into account. However, a translation into (QA)LYs gained was not performed because, within the time frame of this study, not enough reliable data could be gathered to work this out. This does not mean that we consider longer term costs and effects unimportant. On the contrary, we present the impact on various outcomes such as T21 detection, procedure-related pregnancy loss and total number of Down births whether or not after a false negative screening test in a transparent way in order to inform our policy makers. Furthermore, if all harms (procedure-related pregnancy loss and Down birth after a false-negative screening result) are reduced and the cost per diagnosis stays the same, then it becomes difficult to oppose to the introduction and reimbursement of this new technology.

Comparison with other studies

A systematic review of full economic evaluations on the cost-effectiveness of NIPT was performed in December 2013 by searching the websites of HTA institutes and the following databases: CRD HTA, CRD NHS EED, OVID Medline and Embase. Details on the search strategy and selection process are available elsewhere.[9] Seven full economic evaluations were retained.[19-21 28-31] All studies were published recently (2011-2013). Five were performed in the US, one in Australia[29] and one in the UK.[21] An additional economic evaluation from Ontario, Canada, was published during the writing of this article.[18]

The comparator is different across the identified studies and results are as follows:

- *Contingent screening with NIPT versus current practice*: Contingent screening is more efficient than current standard of care, providing benefits at a lower cost.[20 28] In one of these studies, cost savings were obtained by including a cost for Down syndrome.[20] The only study without any explicit conflict of interest concludes that the introduction of NIPT for screening of high-risk pregnancies would result in better outcomes (additional T21 detected, reduced invasive testing and thus less procedure-related fetal losses), while costs would increase with about 10%, which will need further policy planning.[29]
- *Contingent screening with NIPT versus universal NIPT screening*: Contingent screening is more efficient than universal screening.[21 31] The cost for contingent screening is substantially lower than with universal screening.[31] Offering NIPT to all women would only become affordable if the NIPT costs fall substantially.[21]
- *Contingent screening with NIPT versus NIPT as a diagnostic tool*: Contingent screening with NIPT is more efficient than applying NIPT as a diagnostic tool.[19]

Results of the previous studies are unfortunately not easily transferable to the Belgian context for several reasons. The populations described in the economic evaluations differ. Some model the general population[21 31 15 25] of pregnant women[29, 35] while others only include populations at high-risk for T21. Related to this, the interventions and comparators used in the models differ. Not all studies consider NIPT in both first and second line. Only two studies include universal NIPT screening,[21 31] of which one does not include the current situation.[35] Furthermore, the values for several input variables are often not representative for the Belgian situation. For example, the sensitivity of first trimester combined screening (85%) in the study of Song et al.[20], is much higher than in the real-

world Belgian population. As previously mentioned, inclusion of long-term costs and quality of life data should also be supported by better data.

The price of NIPT

The price of NIPT varies widely across the economic evaluations published in 2012 or 2013: $1200 (€880, £713),[28] $795 (€583, £472),[20] AU$743 (€479, £388),[29] and a price in the range of $500-$2000 (€367-€1466, £297-£1187).[21] The costs to perform this test are decreasing. In Belgium, the official price of the university hospital in Leuven is €460 (£373). Sequenom has announced a low cost NIPT of $250 to $300 (€183-€220, £149-£178), to be available by the end of 2014.[32] These changes in prices, together with test accuracy, should be followed in order to take appropriate policy decisions.

Pressure for referral to NIPT

Most triage scenarios published as well as our model start from the combined ultrasound and biochemical screening. If reimbursement can be restricted to the 5% of the screened population using the 1:300 cut-off, this may actually lead to a reduction in overall harms and savings for the health care budget, even at a cost per NIPT of €460. However, in this case, there will be pressure both from physicians and patients, to further lower the threshold for referral to NIPT, officially or informally. Indeed, in absence of rigid quality assessment, the ultrasound part of the current screening remains strongly operator (and machine) dependent. This may lead to an increase of the number of women considered at risk after the current screening and thus eligible for NIPT reimbursement.

Conditions for a successful introduction of NIPT

Providing correct information and counselling and respect for the decision taken by the women or parents remains a cornerstone of any screening process.

As mentioned above the NIPT test does not provide a result in a fraction of women tested. If primary NIPT is offered at gestational week 10 the proportion of 'no result' after a repeat NIPT may be 4% instead of 2%. If most of these women would opt directly for invasive testing instead of falling back to the current screening tests as we assumed, the reduction in harms related to the invasive procedure might not be realised. It is therefore crucial to monitor the performance of the real-life implementation of NIPT not only for sensitivity and specificity, but also for the proportion of 'no results' and the uptake of invasive testing after a 'no result' answer for NIPT in first-line.

The ultrasound should remain a key component of the prenatal screening process also after the introduction of NIPT in second or first line. Women with a fetal NT>3.5 mm (the 99th percentile) are directly (without use of biochemistry information) offered genetic counselling, diagnostic invasive testing and follow-up in keeping with international guidelines.[18] In such cases, there is a greater than 30% risk of chromosomal abnormalities, including but not limited to T21,[16] and other abnormalities such as heart defects.[33 34]

It has repeatedly been recommended that NT based risk assessment should only be implemented in centres with appropriately trained and accredited sonographers using high-quality equipment. Results should be subject to regular audit by an external agency.[16 34] Such requirements are still to be implemented in Belgium. Also the calibration of the ultrasound machines seems to be a problem.[35] For example, an NT of 3.5mm is reported as 3.2mm on one machine and as 3.8mm on another instrument. This finding illustrates the clear need for further standardization of the NT assessment.

We believe that improving the quality of the ultrasound NT assessment in Belgium could increase the overall sensitivity of the screening, e.g. from 72.5% to 77.5% at 95% specificity. This improvement has been modelled separately and confirms that any improvement of the current screening sensitivity is mainly of importance when NIPT is used in second line, reducing the number of T21 cases missed because of a false negative result. It could also help in the acceptance of the current screening as alternative test in cases where NIPT does not provide a result in first line screening. Amniocentesis and CVS carry a 1 to 2% risk of membrane rupture, a 0.3% risk of sustained oligohydramnios,[13] and a 1% risk of induced miscarriage, which may be higher after CVS as compared with amniocentesis.[14 36] It has been suggested that 100 to 400 CVSs are needed before the learning curve reaches a plateau.[36] The risk may thus be lower in the hands of experienced operators and higher in low–volume, less experienced centres. Currently, no required minimum volumes have been defined in Belgium.

Conclusions and policy implications

In comparison with the current prenatal screening for trisomy 21, the appropriate use of NIPT in either first or second line clearly improves the benefit-risk ratio. Based on the availability of data, it was not possible to reliably calculate cost per (QA)LY gained. From an economic point of view, assuming that we accept the current screening situation, we recommend our National Health Insurer to cover the cost of NIPT if the introduction of NIPT does not increase the screening cost per case of trisomy 21 detected. If offered at the current price of €460, NIPT can be introduced as triage test, even if the screening risk cut-off is lowered from 1:300 to 1:600, corresponding to about 9% positive screen results eligible for NIPT reimbursement. Attention should be paid to further increase the quality of current screening with NT. As the number of invasive diagnostic tests will likely decrease, procedures should be centralised. In terms of benefits and harms, the use of NIPT in first line is preferred over its use in second line. However, the cost of NIPT should be lowered to about €150 in order not to increase the screening cost per case of trisomy 21 detected. In Belgium, at this (future) price level, NIPT should be offered to and reimbursed for all pregnant women.

Data sharing statement: No additional data available.

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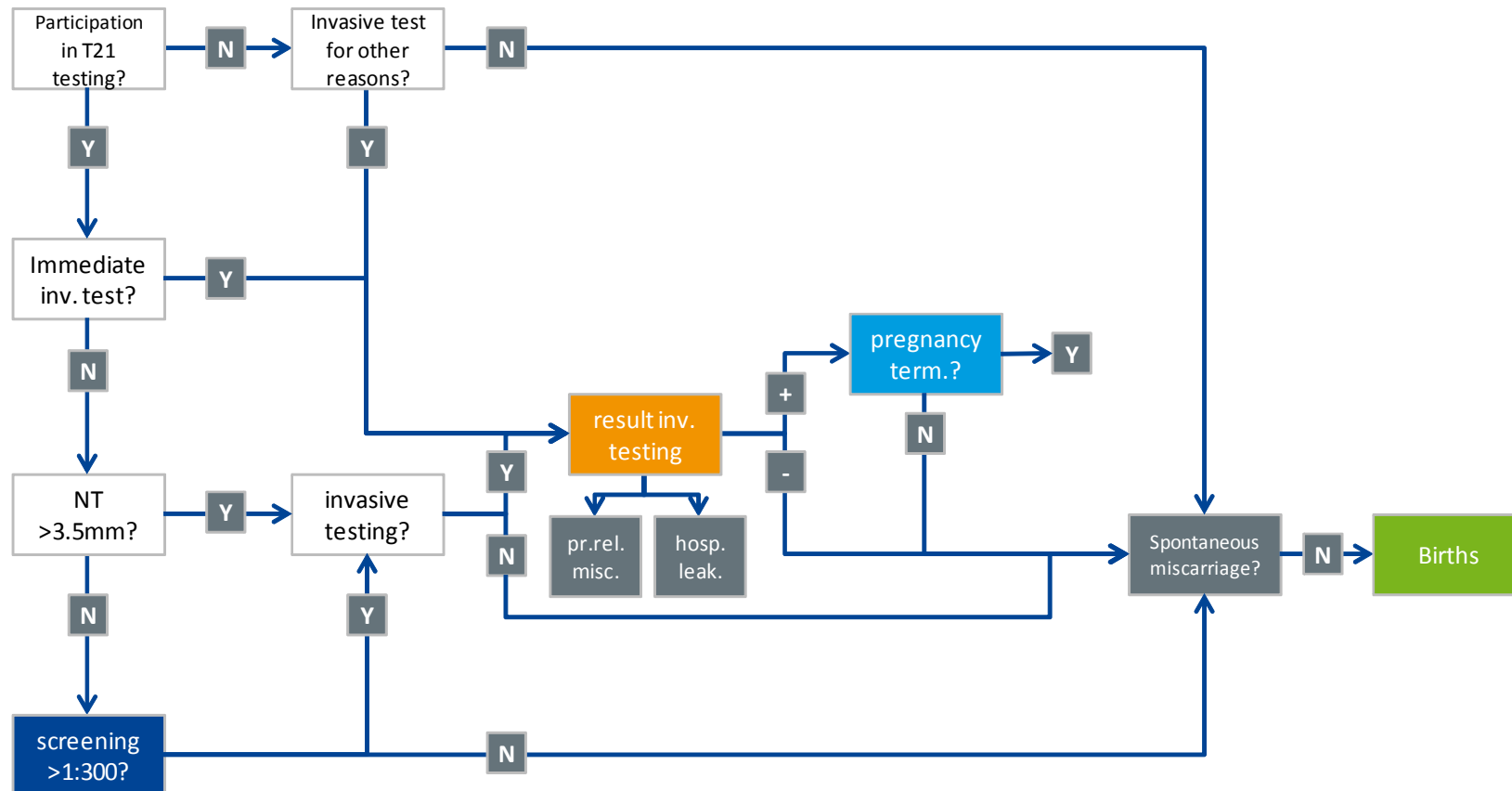
Supplementary material

Modelling of NIPT

Figure 3 presents an overview of the current screening strategy in Belgium. In Figure 4, the current first trimester biochemistry screening and second trimester screening is replaced by NIPT at week 12.

In a separate supplementary file, we present and explain the three models in detail (current screening, NIPT 2nd line and NIPT 1st line) with inclusion of the number of pregnant women and T21 pregnancies at different moments in the model.

Figure 3 – Current screening strategy

Hosp.leak.: hospitalisation for leakage; inv.: invasive; pr.rel.misc.: procedure-related miscarriage; term.: termination.

Figure 4 – Screening strategy with NIPT as first-line test

Hosp.leak.: hospitalisation for leakage; inv.: invasive; pr.rel.misc.: procedure-related miscarriage; rep.: repeat; term.: termination.

Supplementary material

In this supplementary file we transparently present the three screening models: current screening, NIPT 2nd line, and NIPT 1st line. The figures of the models are copies from the original excel file, including exact numbers. These numbers represent (singleton) pregnancies and the number of T21 foetuses is added between brackets. All transitions are mentioned on the figures and explained with a short reference to the full text of the report. Small differences in numbers (maximum 1 unit) might be possible due to the presentation of rounded numbers. In the original calculations, full details with non-rounded numbers were taken into account.

Current screening:

Part 1:

- **1** : 131567 pregnant women at week 10 including 350 T21 foetuses (part 2.1.3.4 and Table 9).

- **2** : Exclusion of 1.8% twin pregnancies (part 2.1.3.3 and Table 9). 129199 singleton pregnancies and 2368 twin pregnancies.

- **3** : Impact of miscarriage between week 10 and 40 (part 2.1.3.4 and Table 9). 2368 x (1-0.05) = 2250, 8 x (1-0.36) = 5.

- **4a** → **4e** : Impact of miscarriage between week 10 and 15 (part 2.1.3.4 and Table 9).

- **5a** , **5b** , **5c** : 1st and 2nd trimester screenings (part 2.1.6.1 and Table 12): number of tests, cost per activity, and % of screening uptake. E.g. 5a) 26 056/129 199 = 20.17%.

- **6a** , **6b** , **6c** : For simplicity, numbers are recalculated to week 14 and we assume that further steps are taken at week 14 (although in reality this might be between week 11 and 20). This has no meaningful impact on results since afterwards spontaneous pregnancy termination is modeled in one step between week 14 and 40.

- **6d** : The remaining pregnant women that did not participate in screening (124 608 – 21 560 – 51 583 – 25 130 = 26 335).

- **7a** , **7b** : Total number of singleton pregnant women (not) participating in screening. Number of T21 fetusses (292 in total) is mentioned between brackets.

- **8a** , **8b** : 398 pregnant women with an ultrasound detected NT>3.5mm are referred directly for invasive testing. They are divided proportionally among the screening (n=314) and no-screening (n=84) participants (see 2.1.6.3). It was assumed that women opting for an invasive test based on NT had an increased prevalence of a T21 pregnancy of 1:10.
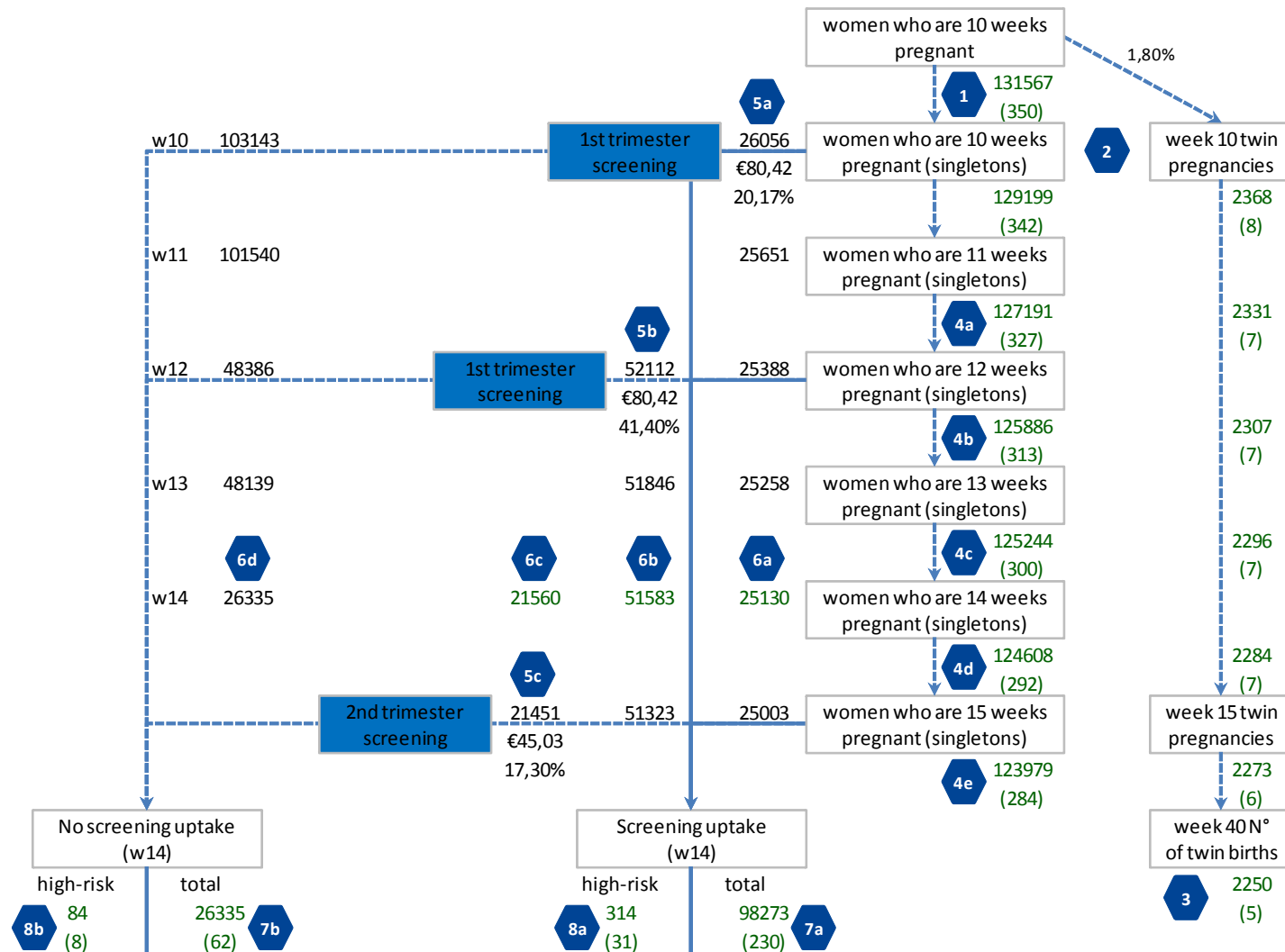
Part 2:

- **9a** , **9b** : Exclusion of the high-risk pregnancies (NT>3.5mm): 26 335 – 84 = 26 251; 98 273 – 314 = 97 959.

- **10a**, **10b**: Results of the current screening. E.g. True negatives: (97 959 – 199) x specificity of 95.0343% = 92 906; True positives: 199 x sensitivity of 72.5352% = 144 (part 2.1.6.1).

- **11a**, **11b**: After a positive screening test result, we assume 87.5% of women chooses to have an invasive diagnostic test (part 2.1.6.3). Thus (4855+144) x 87.5% = 4374.

- **12**: In Belgium, there was a total of 7586 of invasive tests (part 2.1.6.3). This leaves us with 3212 (7586 – 4374) invasive tests. We already identified 398 (314+84) pregnant women with an ultrasound detected NT>3.5mm. We assume another 1000 invasive tests for T21 detection are performed in pregnant women (often at low risk) who wish to have more certainty than can be provided with the current screening, and/or are referred based on age over 35 (despite existing guidelines). The remaining 1814 invasive tests are performed for non-T21 indications, including structural anomalies detected with ultrasound not related to T21 detection. The 1000 and 84 invasive tests are specifically for T21 and were not counted before and represent another 0.87% of the pregnant population. This slightly increase the overall uptake (of any type of) testing for Down from 78.87 to 79.74%.

- **13a**, **13b**: After CVS or amniocentesis, an incremental procedure related fetal loss of on average 1% was assumed in our model (e.g. 4374 x 1% = 44). We also included a 1% risk of hospitalisation for one week for leakage. The costs for such a stay in an acute hospital in Belgium are €3515 (part 2.1.6.3).

- **14**: One of the outcomes in our model is the number of procedure related miscarriages and the number of such miscarriages related to T21 detection. The latter excludes the miscarriages related to the 1814 invasive tests performed for non-T21 indications.

- **15**: In the 'no screening uptake' group, there are 23 437 singleton pregnant women (26 251 – 1000 – 1814 = 23 437).
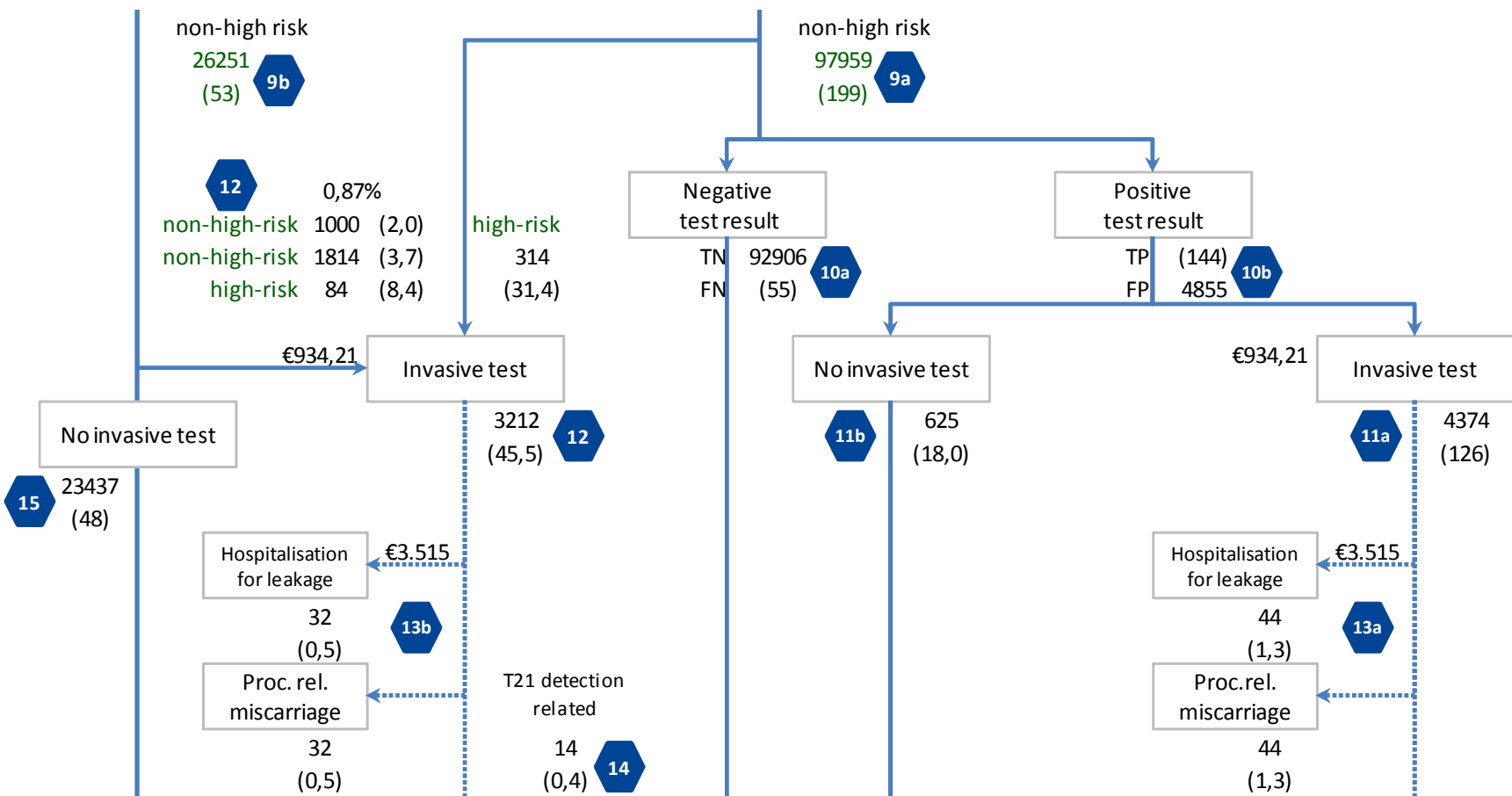
Part 3:

- **16a**, **16b**: In our model we assume the invasive diagnostic test is 100% sensitive and 100% specific (part 2.1.6.3). E.g. (4374 – 126) – (44 – 1.3) = 4205 and 126 – 1.3 = 125.

- **17a**, **17b**: T21 pregnancy termination was induced in 95.45% (part 2.1.6.4). E.g. 125 x 95.5% = 119

- **18a** → **18e**: Spontaneous miscarriage is taken into account (part 2.1.6.5, 2.1.3.4 and Table 9). E.g. 18a) (125 – 119) x 0.25 = 1.4; 4205 x 0.0144 + 1.4 = 62; 18c) 48 x 0.25 = 12; (23 437 – 48) x 0.0144 + 12 = 350.

- **19a** → **19e**: The total number of singleton births at week 40 with the number of Down births between brackets. E.g. 19a) (4205 + 125) – (119 + 62) = 4149; 125 – (119 + 1.4) = 4.3; 19c) 23 437 – 350 = 23 087; 48 – 12 = 35.7.

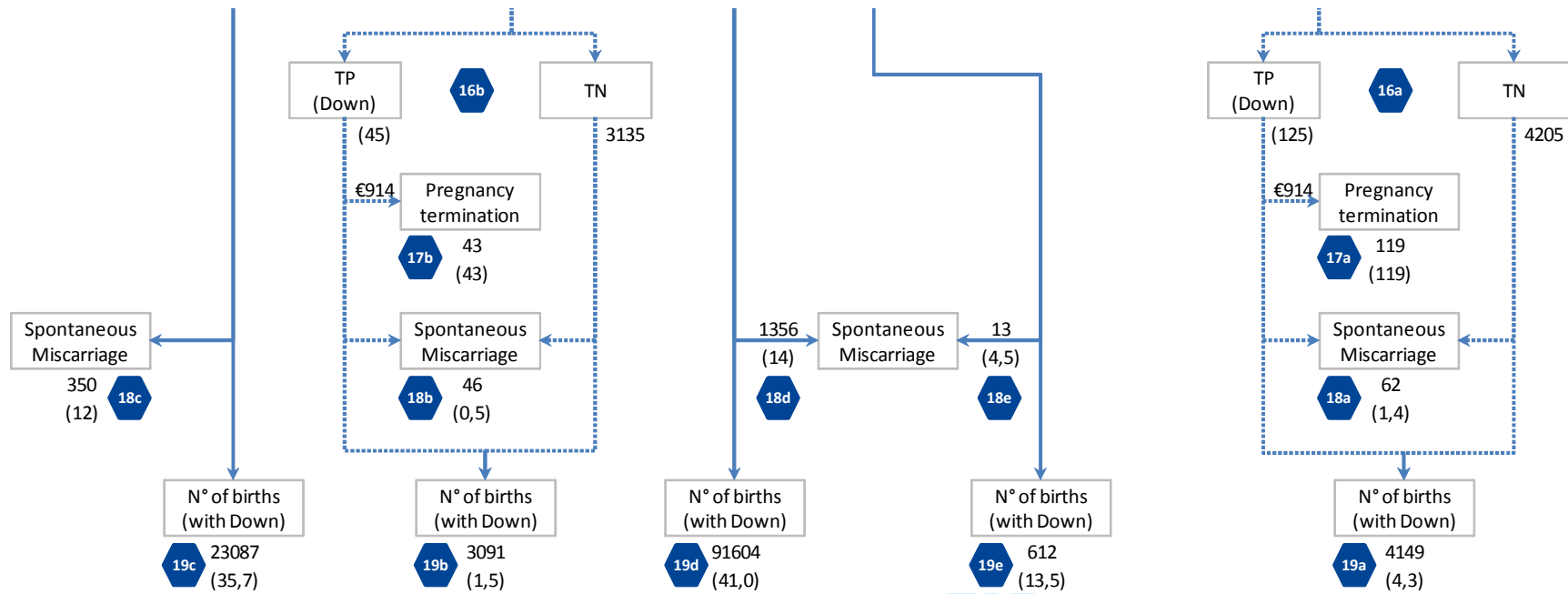Part 1 (current screening)

women who are 10 weeks pregnant

1,80%

1 131567 (350)

5a 26056

2

week 10 twin pregnancies

w10 103143

1st trimester screening €80,42 20,17%

women who are 10 weeks pregnant (singletons)

129199 (342)

2368 (8)

w11 101540 25651

women who are 11 weeks pregnant (singletons)

4a 127191 (327)

2331 (7)

5b 52112

w12 48386 25388

1st trimester screening €80,42 41,40%

women who are 12 weeks pregnant (singletons)

4b 125886 (313)

2307 (7)

w13 48139 51846 25258

women who are 13 weeks pregnant (singletons)

4c 125244 (300)

2296 (7)

6d **6c** 21560 **6b** 51583 **6a** 25130

w14 26335

women who are 14 weeks pregnant (singletons)

4d 124608 (292)

2284 (7)

5c 21451

2nd trimester screening €45,03 17,30%

51323 25003

women who are 15 weeks pregnant (singletons)

week 15 twin pregnancies

4e 123979 (284)

2273 (6)

No screening uptake (w14)

Screening uptake (w14)

week 40 N° of twin births

high-risk   total

high-risk   total

8b 84 (8)

26335 (62) **7b**

8a 314 (31)

98273 (230) **7a**

3 2250 (5)

Part 2 (current screening)

non-high risk

26251

(53) **9b**

non-high risk

97959

(199) **9a**

12   0,87%

non-high-risk   1000   (2,0)   high-risk

non-high-risk   1814   (3,7)   314

high-risk   84   (8,4)   (31,4)

Negative
test result

TN   92906   **10a**

FN   (55)

Positive
test result

TP   (144)   **10b**

FP   4855

€934,21   Invasive test

3212   **12**

(45,5)

No invasive test

11b   625

(18,0)

€934,21   Invasive test

11a   4374

(126)

No invasive test

15   23437

(48)

Hospitalisation
for leakage

32   **13b**

(0,5)

Proc. rel.
miscarriage

32

(0,5)

T21 detection
related

14   **14**

(0,4)

€3.515

Hospitalisation
for leakage

44   **13a**

(1,3)

Proc.rel.
miscarriage

44

(1,3)

€3.515

Part 3 (current screening)

TP (Down)	**16b**	TN	
(45)		3135	

€914 → Pregnancy termination
17b 43 (43)

Spontaneous Miscarriage
18c 350 (12)

Spontaneous Miscarriage
18b 46 (0,5)

1356 (14) → Spontaneous Miscarriage ← 13 (4,5)

N° of births (with Down)
19c 23087 (35,7)

N° of births (with Down)
19b 3091 (1,5)

N° of births (with Down)
19d 91604 (41,0)

N° of births (with Down)
18d / **18e**

N° of births (with Down)
19e 612 (13,5)

TP (Down)	**16a**	TN	
(125)		4205	

€914 → Pregnancy termination
17a 119 (119)

Spontaneous Miscarriage
18a 62 (1,4)

N° of births (with Down)
19a 4149 (4,3)

NIPT 2nd line:
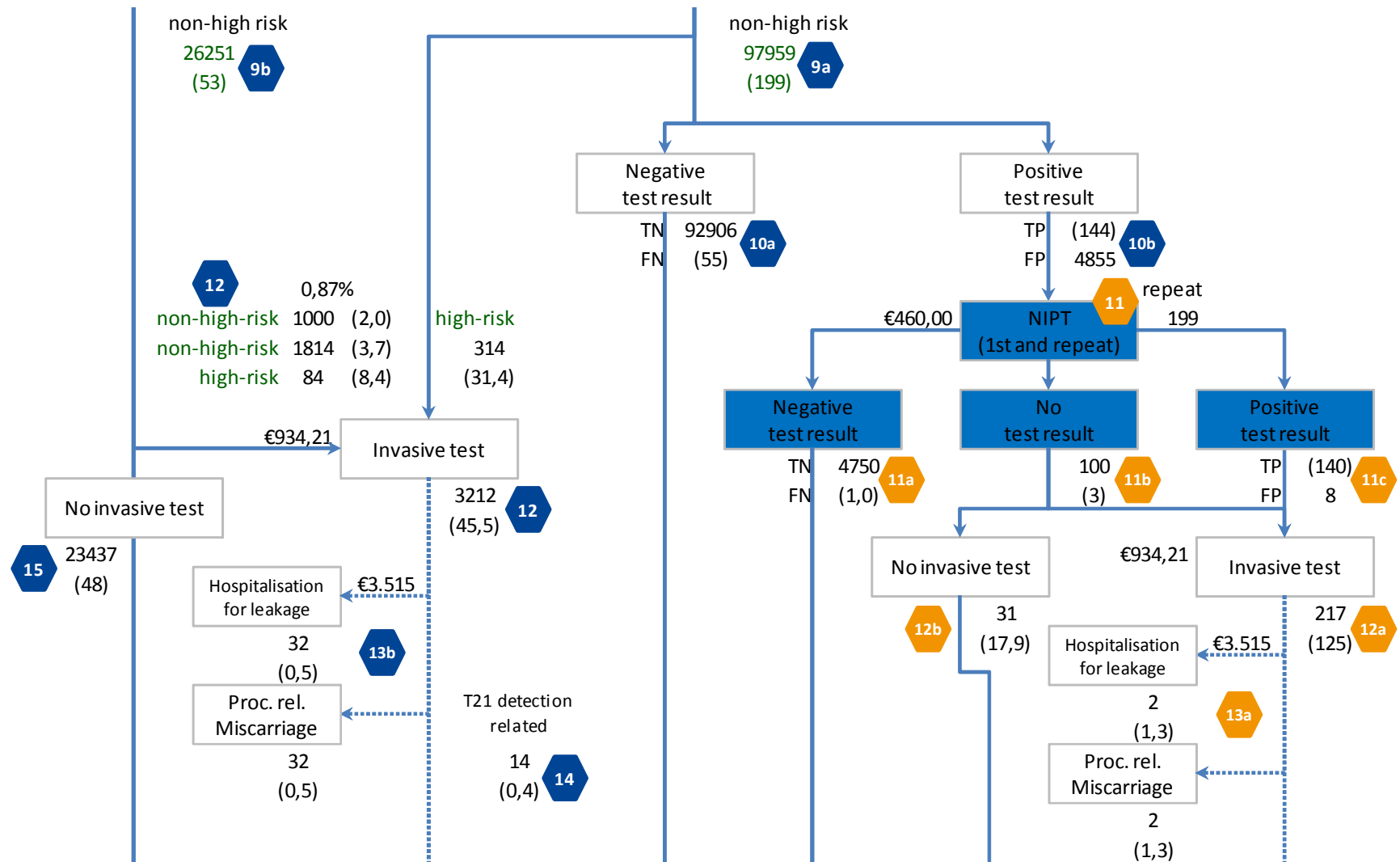
Part 1:

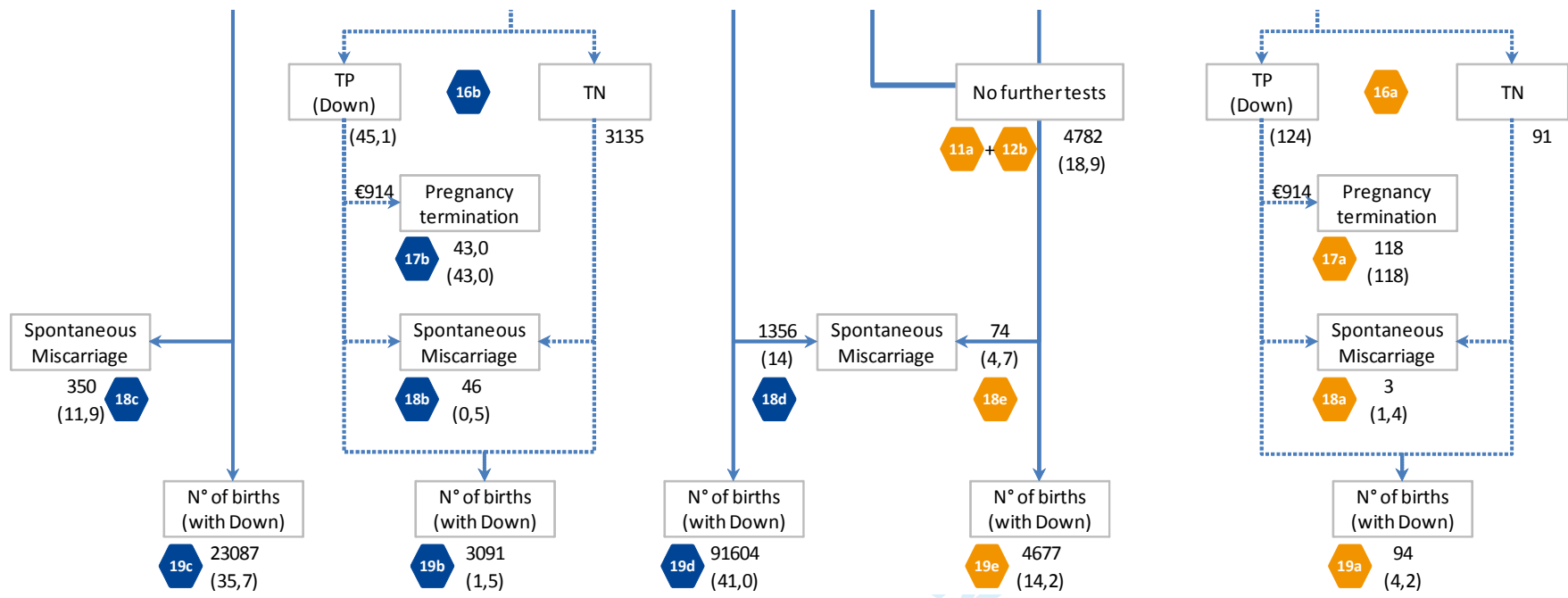- ⬡**1** → ⬡**8b** : See current screening

Part 2:

- All blue hexagons: See current screening

- ⬡**11** : NIPT is offered to 4999 (4855+144) women at increased risk after current screening (part 2.1.4.2). We assume the first NIPT is repeated in 4% of cases. We assume the second NIPT test is performed about one week later and therefore also take into account the number of miscarriage during 1 week (4999 x 4% x (1 – (0.015 – 0.01)) = 199). Each NIPT test costs €460 (part 2.1.6.2).

- ⬡**11a** , ⬡**11b** , ⬡**11c** : We assume that after repeat testing there is no result in 2% of cases: 11b) 4999 x 2% = 100; 144 x 2% = 3. For the remaining 98% the results of NIPT screening are calculated: E.g. True negatives: (4855 x specificity of 99.84%) x (98%) = 4750; True positives: (144 x sensitivity of 99.30%) x (98%) = 140 (part 2.1.6.2).

- ⬡**12a** , ⬡**12b** : After a positive NIPT screening test result or no NIPT result (but previously a positive test result after current screening), we assume 87.5% of women chooses to have an invasive diagnostic test (part 2.1.6.3). Thus (100 + 140 + 8) x 87.5% = 217.

- ⬡**13a** : Same reasoning as for ⬡**13a** (1% hospitalisations for leakage and 1% procedure related miscarriages) but with other underlying numbers as mentioned on the figure.

Part 3:

- All blue hexagons: See current screening

- ⬡**16a** → ⬡**19e** : same reasoning as for ⬡**16a** → ⬡**19e** but with other underlying numbers as mentioned on the figure.

Part 2 (NIPT 2nd line)

non-high risk
26251
(53) **9b**

non-high risk
97959
(199) **9a**

Negative
test result

TN 92906 **10a**
FN (55)

Positive
test result

TP (144) **10b**
FP 4855

12 0,87%
non-high-risk 1000 (2,0)
non-high-risk 1814 (3,7)
high-risk 84 (8,4)

high-risk
314
(31,4)

€460,00 NIPT **11** repeat
(1st and repeat) 199

€934,21 Invasive test

3212 **12**
(45,5)

Negative
test result

TN 4750 **11a**
FN (1,0)

No
test result

100 **11b**
(3)

Positive
test result

TP (140) **11c**
FP 8

No invasive test

15 23437
(48)

Hospitalisation
for leakage

32 **13b**
(0,5)

Proc. rel.
Miscarriage

32
(0,5)

T21 detection
related

14 **14**
(0,4)

No invasive test

12b 31
(17,9)

€934,21 Invasive test

217 **12a**
(125)

€3.515 Hospitalisation
for leakage

2 **13a**
(1,3)

Proc. rel.
Miscarriage

2
(1,3)

€3.515

Part 3 (NIPT 2nd line)

TP (Down)	**16b**	TN		
(45,1)		3135		

No further tests
11a + **12b**   4782
(18,9)

TP (Down)	**16a**	TN	
(124)		91	

€914   Pregnancy termination
17b   43,0
(43,0)

€914   Pregnancy termination
17a   118
(118)

Spontaneous Miscarriage
350
18c   (11,9)

Spontaneous Miscarriage
18b   46
(0,5)

1356
(14)   Spontaneous Miscarriage   74
(4,7)
18d   **18e**

Spontaneous Miscarriage
18a   3
(1,4)

N° of births (with Down)
19c   23087
(35,7)

N° of births (with Down)
19b   3091
(1,5)

N° of births (with Down)
19d   91604
(41,0)

N° of births (with Down)
19e   4677
(14,2)

N° of births (with Down)
19a   94
(4,2)

NIPT 1st line:

Part 1:

- All blue hexagons: See current screening
- **5a**, **5b**, **5c**: The current first and second trimester screening is replaced by NIPT and we assume the NIPT is performed at week 12 (part 2.1.4.3). Taking into account the number of spontaneous miscarriages, recalculating 98 273 singleton pregnant women from week 14 to 12 results in 99 281 pregnant women. Furthermore, we assume that the 1000 women who are directly referred to invasive testing based on age (despite existing guidelines) or the wish to have more certainty than can be provided with the current testing, will now opt to have a NIPT test. Recalculating from week 14 to 12, this results in 1010 extra NIPT tests.
- **6**: One week later, 3991 repeat tests are performed (98 774 + 1005) x 4% = 3991.

Part 2:

- All blue hexagons: See current screening.
- **5**: see **5a** in part 1.
- **9a**: The 314 pregnant women with an ultrasound detected NT>3.5mm continue to be referred directly for invasive testing (part 2.1.4.3). The 1000 extra NIPT tests are taken into account, thus 98 273 – 314 + 1000 = 98 959.
- **10a**, **10b**, **10c**: We assume that after repeat testing there is no result in 2% of cases: 10b) 98 959 x 2% = 1979; 201 x 2% = 4. For the remaining 98% the results of NIPT screening are calculated: E.g. True negatives: ((98 959 – 201) x specificity of 99.84%) x (98%) = 96 628; True positives: (201 x sensitivity of 99.30%) x (98%) = 196 (part 2.1.6.2).
- **11**: In case no NIPT result is obtained after a repeat NIPT the current screening strategy is applied (part 2.1.4.3).
- **11a**, **11b**: Results of the current screening. E.g. True negatives: (1979 – 4) x specificity of 95.0343% = 1877; True positives: 4 x sensitivity of 72.5352% = 2.9 (part 2.1.6.1).
- **12a**, **12b**: After a positive NIPT screening test result or a positive current screening test result (after a NIPT no result), we assume 87.5% of women chooses to have an invasive diagnostic test (part 2.1.6.3). Thus (196 + 155 + 2.9 + 98) x 87.5% = 395.
- **12c**: The number of invasive tests in the 'no screening uptake' arm is 2212 instead of 3212 (excluding those 1000 pregnant women: see point 5).
- **13a** → **14**: same reasoning as for **13a** → **14** but with other underlying numbers as mentioned on the figure.

Part 3:

- All blue hexagons: See current screening.

- **16a** → **19f** : same reasoning as for **16a** → **19e** but with other underlying numbers as mentioned on the figure.

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Part 1 (NIPT 1st line)

women who are 10 weeks pregnant

1,80%

1 131567
(350)

women who are 10 weeks pregnant (singletons)

2

week 10 twin pregnancies

129199
(342)

2368
(8)

women who are 11 weeks pregnant (singletons)

2331
(7)

4a 127191
(327)

5c
1010

1st NIPT

99281
€460,00

women who are 12 weeks pregnant (singletons)

w12   26605

2307
(7)

4b 125886
(313)

5b
1005

6

repeat NIPT

3991
€460,00

98774

women who are 13 weeks pregnant (singletons)

w13   26470

2296
(7)

4c 125244
(300)

extra
1000

5a

98273

women who are 14 weeks pregnant (singletons)

w14   26335

4d 124608
(292)

2284
(7)

women who are 15 weeks pregnant (singletons)

week 15 twin pregnancies

2273
(6)

4e 123979
(284)

week 40 N° of twin births

No screening uptake (w14)

Screening uptake (w14)

high-risk   total

high-risk   total

3 2250
(5)

8b 84
(8)

26335
(62) 7b

8a 314
(31)

98273
(230) 7a

Part 2 (NIPT 1ˢᵗ line)

non-high risk
26251
(53) **9b**

5

non-high-risk	1000	(2,0)
non-high-risk	1814	(3,7)
high-risk	84	(8,4)

high-risk
314
(31,4)

non-high risk
98959
(201) **9a**

Negative test result
TN 96628 **10a**
FN (1,4)

No test result
1979 **10b**
(4)

Positive test result
TP (196) **10c**
FP 155

€934,21 → Invasive test

No invasive test
15 23437
(48)

2212 **12c**
(43,5)

Hospitalisation for leakage
22 **13b**
(0,4)

Proc. rel. Miscarriage
22
(0,4)

€3.515

T21 detection related
4
(0,4) **14**

€45,03
11 Current screening

Negative test result
TN 1877 **11a**
FN (1,1)

Positive test result
TP (2,9) **11b**
FP 98

No invasive test
56 **12b**
(24,8)

€934,21 → Invasive test
395 **12a**
(174)

Hospitalisation for leakage
4 **13a**
(1,7)

€3.515

Proc. rel. Miscarriage
4
(1,7)

Part 3 (NIPT 1st line)

TP (Down) (43,0)	**16b**	**TN** 2147	

€914 → **Pregnancy termination** **17b** 41,1 (41,1)

Spontaneous Miscarriage **18b** 32 (0,5)

Spontaneous Miscarriage **18c** 350 (11,9)

1396 (0,3) → **Spontaneous Miscarriage** **18d** ← 27 (0,3)

Spontaneous Miscarriage **18e**

Spontaneous Miscarriage **18f** ← 6,7 (6,2)

TP (Down) (172)	**16a**	**TN** 219	

€914 → **Pregnancy termination** **17a** 164 (164)

Spontaneous Miscarriage **18a** 5 (2,0)

N° of births (with Down) **19c** 23087 (35,7)

N° of births (with Down) **19b** 2117 (1,5)

N° of births (with Down) **19d** 95233 (1,0)

N° of births (with Down) **19e** 1851 (0,8)

N° of births (with Down) **19f** 50 (18,6)

N° of births (with Down) **19a** 222 (5,9)

Supplementary material

Scenario analyses

Several scenario analyses are modelled:

- In Belgium, the overall uptake (of any type of) testing for Down is currently about 80%. If NIPT would be offered in first line, there is a possibility that the screening uptake of primary NIPT will be higher than for the current screening. A large survey in the UK suggests an uptake of primary NIPT of 88.2% (972/1103; 95%CI 86.1–90%), including respondents who would currently decline T21 screening.[37] A scenario with 90% NIPT uptake in first line is presented without changing any other input variable (see Table 4).
- In the reference case, the price of NIPT is set at €460. If NIPT would be used in 1st line, the eligible population would be much larger and scale effects could result in lower prices. Also evolution in technology will help. A threshold analysis is performed, changing the price of NIPT to keep the short-term costs per case of T21 detected at the same level as in the current screening scenario. This price was about €150. Results with this lower price are presented in Figure 2 and Table 4.
- In the reference case, a cut-off risk of 1:300 for T21 is used. Based on Belgian context-specific data, this results in a referral of about 5% of all pregnant women for definitive prenatal diagnosis using an invasive test, while the sensitivity is 72.5% (AML data). Lowering of the threshold is considered in the NIPT triage scenario. The cut-off risk with specificity closest to 95% (1:300), 90% (1:600), 85% (1:1100), 80% (1:1700) and 75% (1:2400) were selected plus the lowest reported cut-off risk of 1:3000 which has a specificity of 71%. Sensitivity and specificity are modelled with beta distributions reflecting the parameters from the AML data (see Table 5). Results are presented in Table 6.
- In Belgium, based on expert opinion, the sensitivity of the current screening could be improved by increasing the quality of the current screening, especially the quality of the nuchal translucency measure. An absolute increase of 5% in the current screening sensitivity was applied to model this, i.e. being 77.5% instead of 72.5%, without changing specificity. These results are also presented in Table 6.

Table 4 – Changing the uptake and price of NIPT

Test strategy uptake	NIPT 1st line 80%	NIPT 1st line 90%	NIPT 1st line 80%	NIPT 1st line 90%
	NIPT = €460		NIPT = €150	
(Down) births, diagnosis and miscarriages				
N° of births	122560	122542	122560	122542
N° of Down born	63	45	63	45
N° of Down born (false neg. screening)	2	2	2	2
N° of T21 detected	215	240	215	240
N° of proc.rel. miscarriages	26	27	26	27
N° of T21 proc.rel. misc.	8	8	8	8
Costs for testing during pregnancy				
1st & 2nd trim. screening cost	€89.123	€100.718	€89.123	€100.718
NIPT cost	€47.969.932	€54.191.054	€15.642.369	€17.670.996
Cost invasive tests	€2.435.614	€2.486.645	€2.435.450	€2.486.456
Cost hosp.leakage & pregn.term.	€279.698	€303.489	€279.539	€303.308
Total cost (Short term)	**€50.774.367**	**€57.081.906**	**€18.446.482**	**€20.561.478**
Short term cost/T21 detected	**€236.247**	**€237.916**	**€85.897**	**€85.769**
Extra cost per extra T21 detected	€1.038.119	€712.092	€118.870§	€106.160§

Proc.rel. misc.: procedure-related miscarriage; § The extra cost per extra case of T21 diagnosed was compared with NIPT 2nd line (i.e. the previous best alternative) but with a price of €460 for NIPT (we assume such a lower price would in first instance only be probable with high volumes of NIPT such as in 1st line).

Table 5 – sensitivity and specificity of 1st and 2nd trimester screening related to the cut-off risk

Cut-off risk	Sensitivity	Uncertainty	Specificity	Uncertainty
1:300	72.54%	Beta(103;39)	95.03%	Beta(117 144; 6121)
1:600	80.99%	Beta(115;27)	90.88%	Beta(112 018; 11 247)
1:1100	84.51%	Beta(120;22)	85.41%	Beta(105 283; 17 982)
1:1700	87.32%	Beta(124;18)	80.17%	Beta(98 817; 24 448)
1:2400	87.32%	Beta(124;18)	75.18%	Beta(92 675; 30 590)
1:3000	88.73%	Beta(126;16)	71.46%	Beta(88 087; 35 178)

Source: AML data

Table 6 – Varying the sensitivity of the current screening approach or risk cut-off if NIPT is used in 2nd line

Test strategy	Current screening	Current with 77.5% sensitivity	NIPT 2nd line (1/300)	NIPT 2nd line (1/600)	NIPT 2nd line (1/1100)	NIPT 2nd line (1/1700)	NIPT 2nd line (1/2400)	NIPT 2nd line (1/3000)
(Down) births, diagnosis and miscarriages								
N° of births	122543	122546	122554	122529	122509	122490	122476	122463
N° of Down born	96	90	97	86	82	78	78	77
N° of Down born (false neg. screening)	41	34	42	29	24	20	20	18
N° of T21 detected	170	178	169	184	190	194	194	197
N° of proc.rel. miscarriages	76	34	34	35	36	37	38	39
N° of T21 proc.rel. misc.	58	16	16	17	18	19	20	21
Costs for testing during pregnancy								
1st & 2nd trim. screening cost	€7.252.215	€7.252.215	€7.252.215	€7.252.215	€7.252.215	€7.252.215	€7.252.215	€7.252.215
NIPT cost	€0	€2.395.686	€2.390.929	€4.343.507	€6.901.721	€9.357.267	€11.687.078	€13.428.890
Cost invasive tests	€7.086.886	€3.211.490	€3.203.417	€3.288.763	€3.388.650	€3.483.651	€3.569.545	€3.636.013
Cost hosp.leakage & pregn.term.	€415.728	€276.151	€268.375	€284.228	€293.214	€301.016	€304.292	€308.923
Total cost (Short term)	**€14.754.829**	**€13.135.542**	**€13.114.935**	**€15.168.714**	**€17.835.800**	**€20.394.149**	**€22.813.130**	**€24.626.040**
Short term cost/T21 detected	**€86.944**	**€74.063**	**€77.696**	**€82.746**	**€94.188**	**€105.016**	**€117.474**	**€125.249**
Extra cost per extra T21 detected	/	/	/§§	€142.110	€442.346	€531.269	/§§§	€1.750.512

Proc.rel. misc.: procedure-related miscarriage; § This is calculated in a deterministic way since the simulations fall into different quadrants making the average of all simulations unreliable. §§ This is the initial comparator, thus no extra cost per extra T21 detected is calculated. §§§ Due to the same sensitivity and a lower specificity in comparison with the previous situation (based on the data of AML), this scenario is an example of extended dominance.

Table

Table 1| **CHEERS checklist—Items to include when reporting economic evaluations of health interventions**

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	p1, line 5
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	p3, line 3-31
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	p5, line 4-33
		Present the study question and its relevance for health policy or practice decisions.	p5, line 35-45
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	p6, line 16-31
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	p6, line 35-42
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	p5, line 53-56
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	p6, line 34-37
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	p6, line 3-7
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	p6, line 4
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	p6, line 8-13
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	p7, line 3-19
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	not applicable
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	p6, line 48-50
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	p6, line 48 p10, line 18
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	p5, line 49-51
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	assumptions mentioned in relevant parts
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	p8, line 10-35
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	tables p9+p10
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	p12, line 7-52
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	see 20b

(continued)

Section/item	Item No	Recommendation	Reported on page No/line No
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	p12, line 54 - p13, line 50
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	not applicable
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	p13, line 54 - p17, line 35
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	p2, line 10-13
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	p2, line 15

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

BMJ Open

Introducing the non-invasive prenatal test for trisomy 21 in Belgium: a cost-consequences analysis

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2014-005922.R1
Article Type:	Research
Date Submitted by the Author:	23-Sep-2014
Complete List of Authors:	Neyt, Mattias; Belgian Health Care Knowledge Centre (KCE), Hulstaert, Frank; Belgian Health Care Knowledge Centre (KCE), Gyselaers, Wilfried; Hospital Oost-Limburg, Department of Obstetrics and Gynecology; Hasselt University,
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Cost-Benefit Analysis, Diagnostic Techniques, Obstetrical and Gynecological, Down Syndrome, Prenatal diagnosis < OBSTETRICS

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Manuscripts

Introducing the non-invasive prenatal test for trisomy 21 in Belgium: a cost-consequences analysis

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Abstract

Background: First and second trimester screening for trisomy 21 (T21) is reimbursed for all pregnant women in Belgium. Using a cut-off risk of 1:300 for T21, about 5% of all pregnant women are referred for definitive prenatal diagnosis using an invasive test, at a sensitivity of (only) 72.5%. Sensitivity and specificity of the non-invasive prenatal test (NIPT) are over 99% but comes at a cost of €460 (£373) per test. The objective is to estimate the consequences of introducing NIPT for the detection of T21.

Methods: A cost-consequences analysis was performed presenting the impact on benefits, harms and costs. Context-specific real-world information was available to set up a model reflecting the current screening situation in Belgium. This model was used to construct the 2nd and 1st line NIPT screening scenarios applying information from the literature on NIPT's test accuracy.

Results: Introducing NIPT in 1st and 2nd line reduces harm by decreasing the number of procedure-related miscarriages after invasive testing. Offering NIPT in 1st line additionally will miss fewer cases of T21 due to less false negative test results. The introduction of NIPT in 2nd line results in cost savings which is not true for NIPT at current price in 1st line. If NIPT is offered to all pregnant women, the price should be lowered to about €150 to keep the screening cost per T21 diagnosis constant.

Conclusions: In Belgium, introduction and reimbursement of NIPT as 2nd line triage test significantly reduces procedure-related miscarriages without increasing short-term screening costs. Offering and reimbursing NIPT in 1st line to all pregnant women is preferred in the long-term, as it would in addition miss fewer cases of T21. However, taking into account the governmental limited resources for universal reimbursement, the price of NIPT should first be lowered substantially before this can be realized.

Strengths and limitations of this study

- The major strength of the model is the availability of context-specific real-world information and the ability to reflect the current Belgian screening situation by calibrating the model to the number of women screened, the expected and observed number of children born with Down syndrome and the number of invasive tests performed in Belgium. This calibration assures that the initial screening model reflects the current Belgian screening situation as well as possible.

- The most important limitation of our analysis is, due to a lack of reliable data, the inability to apply a long-term horizon and translate outcomes to incremental cost-effectiveness ratios expressing results in euros per (quality-adjusted) life-year gained. However, by presenting the consequences of screening in a transparent way (which includes both the detection of T21, the number of Down births whether or not after a false negative screening test, and the number of procedure-related losses), we try to inform policy makers in a transparent way about the possible consequences of introducing NIPT in different settings.

- In order to avoid a "black box" and to provide other researchers with the possibility to use and adopt the model to their context, details of the full model are included in supplementary files with a step by step explanation for every transition.

Introduction

Prenatal diagnosis of Down syndrome allows for informed decision making with regard to pregnancy continuation or termination. Multiple prenatal trisomy 21 (T21, Down syndrome)/aneuploidy screening strategies in the first and second trimester have been developed.[1] The most commonly used approach for first trimester screening in Belgium is the combination of the nuchal translucency (NT) ultrasound measure at week 12 (week 11-14), the level of free-beta-hCG (human chorionic gonadotrophin hormone) and PAPP-A (pregnancy associated plasma protein-A), in combination with age and medical history. The T21 screening in Belgium is fully reimbursed for all pregnant women and has a high uptake of nearly 80%. However, the overall sensitivity is rather low (~72.5%) compared with reports from neighbouring countries. This moderate performance is likely related to the absence of an obligatory quality assurance system for the nuchal translucency assessment in Belgium.

The non-invasive prenatal testing (NIPT) is performed on a blood sample of the pregnant woman containing circulating cell free DNA both from the mother and the placenta, which in nearly all cases is representative for the foetal DNA. NIPT has been shown to be highly accurate in the detection of common foetal autosomal trisomies, especially T21.[1] However, about 4% of the tests will not provide a result (reduced by half after repeated sampling). The 'no result' NIPT is often caused by a low proportion of foetal DNA, as seen when the sample is obtained before gestational week 12 or in obese women. In dizygotic twin pregnancies NIPT also remains a challenge. Because of its high cost NIPT was originally positioned as a triage test in pregnancies referred for invasive testing (chorionic villus sampling (CVS) or amniocentesis) because of a calculated risk, e.g. above 1:300. NIPT for primary screening (at week 12) of pregnant women with a NT under 3.5mm is becoming a real possibility in view of the growing number of validation studies in low risk pregnancies[2] and especially the prospect of a lower cost per test.

As part of its government-approved work programme, the Belgian Health Care Knowledge Centre (KCE) performed an economic evaluation of introducing NIPT in prenatal diagnosis of Down syndrome. The research questions were the following: 1) What is the impact of introducing NIPT on the benefits and harms of screening for trisomy 21 in the Belgian context? Benefits can be expressed in terms of detection of trisomy 21 such that informed decision making is possible. Possible harms in the process include membrane rupture with amniotic fluid leakage or miscarriage after an invasive test, and the risk of missing the detection of Down syndrome because of a false negative test result. 2) What is the impact on costs and budget for the health insurance of introducing NIPT? What is the cost for the detection of a case of trisomy 21 after introducing NIPT?

Methods

A time-dependent multi-stage transition probability model was developed in Excel in order to assess the consequences of introducing NIPT. This model allows following pregnant women during the screening process and pregnancy up to birth, taking into account e.g. spontaneous miscarriage rates. In accordance with the Belgian guidelines for economic evaluations,[3] the analysis includes direct health care costs from the perspective of the health care payer. Payments out of the public health care budget as well as patients' co-payments are included.

A short-term time horizon was applied in which costs and effects before birth were considered. Due to this short-term horizon, no discount rate was applied. A long-term horizon translating results in extra costs per (quality-adjusted) life year ((QA)LY) gained was not modelled due to a lack of reliable data and thus the hypothetical character of this scenario. In this cost-consequences analysis, the following outcomes were calculated: total number of live births and number of children born with Down syndrome, cases of T21 diagnosed during pregnancy, children with Down syndrome born after a false-negative screening result, procedure-related miscarriages (related to T21 detection), short-term screening cost, short-term screening cost per case of T21 diagnosed, and incremental cost per extra case of T21 diagnosed.

Population

The model includes all pregnancies in the Belgian population, except for twin pregnancies. These represent 1.8% of pregnancies and correspond to about 2.1% of all T21 cases.[4 5] Complete and up to date data from Flanders, the northern community of Belgium representing 54% of the children born in Belgium, were extrapolated to the Belgian situation. The model takes into account the different probabilities of a spontaneous loss of the foetus, for T21 and non-T21 pregnancies, adjusted for gestational week (e.g. 5% and 36% at week 10 for all and T21-pregnancies, respectively (see Table 1)).[6 7] A total of 122,739 births in Belgium in 2012 thus corresponds to 129,199 singleton pregnancies at gestational week 10. The observed live birth prevalence of Down syndrome in Belgium, extrapolated from the Flanders registry, was estimated at 98 in 2012, of which 96 after singleton pregnancies. Based on the age distribution of the pregnant women in Flanders and reported age related prevalence of Down syndrome,[8] 219 T21 singleton live births would be expected without screening, corresponding to 342 pregnancies at week 10. These numbers of expected and observed births of children with Down syndrome were used to calibrate the model.[9]

Comparators

The current practice in Belgium for first and second trimester screening for T21 is modelled and serves as the initial comparator. NIPT is the intervention under consideration and is considered both as a contingent test (i.e. as triage or 2nd line test) and for primary screening (i.e. as 1st line test). Figure 1 presents the triage scenario in which NIPT is offered only to women at increased risk (>1:300) after current screening. The risk cut-off is changed in modelled scenario analyses (see part 'Uncertainty and scenario analyses'). The figures representing the current Belgian screening strategy and NIPT in 1st and 2nd line are presented as supplementary material.

Insert Figure 1 around here: 'Figure 1 – Screening strategy with NIPT as triage test'
Hosp.leak.: hospitalisation for leakage; inv.: invasive; pr.rel.misc.: procedure-related miscarriage; rep.: repeat; term.: termination.

Input variables

The values and probabilities of all input variables in the models are provided in Table 1. Costs for screening, adverse events and pregnancy termination are included and are expressed in € for the year 2013 (Table 2). These costs are based on data from our National Institute for Health and Disability Insurance (NIHDI).

Based on reimbursement data from NIHDI for the year 2011, excluding the 1.8% twin pregnancies, 78,168 pregnant women participate in first trimester screening (€80.42 per activity) and another 21,451 in second trimester screening (€45.03 per activity). The fee for these activities is exclusive of the ultrasound but includes the counselling which is performed by the health care worker offering antenatal screening. NIPT is no replacement of the ultrasound screening and thus no incremental impact on ultrasound screening is included in the model. After adjustments for gestational week, the total screening uptake is estimated at 78.87%. If we also assume 1000 women who immediately undergo invasive testing for T21, the overall uptake of any type of testing for Down syndrome increases to 79.74%. In the reference case, this screening uptake is kept constant.

Sensitivity and specificity of screening at different risk cut-offs are based on the receiver operator characteristics (ROC) curve data from AML (Algemeen Medisch Laboratorium bvba), a large laboratory covering 40% of the first and second trimester screenings for Down syndrome in Flanders. In the reference case, a risk cut-off level of 1:300 is applied, which results in a sensitivity of 72.54% (95%CI: 0.649 – 0.795) and specificity of 95.03% (95%CI: 0.949 – 0.952). This is varied in modelled scenario analyses (see part 'Uncertainty and scenario analyses').

The baseline cost for NIPT (and also for a repeat NIPT if needed) is set at €460, i.e. the current price charged by the University Hospital of Leuven in Belgium. We assume a no first time NIPT result in 4% (3-7%) of cases, reduced to 2% (1-3%) after a repeat NIPT. These estimates are in agreement with 11 studies reviewed by Benn et al.[10] In the primary NIPT model we assume these 2% of women tested will accept to fall back on the current screening and not opt directly for an invasive test. Based on an overview of existing evidence, the sensitivity and specificity of NIPT tests with a result is assumed to be 99.3% (95%CI: 98.2-99.8%) and 99.84% (95%CI: 99.69-99.92%), respectively.[10] No additional cost for NIPT counselling is included since it is assumed that this would happen in a similar way as in the current screening approach and thus does not occur as an incremental cost.

Invasive diagnostic testing is recommended after a positive current screening test or NIPT result in order to confirm the results. The proportion of women undergoing an invasive test after a positive screening was 86.9% (95%CI: 83.9-89.5%) in a large study in Paris.[11] We use a similar probability of 87.5% (80-95%) which was obtained after model calibration. Having no real-world data at our disposal, this proportion of women undergoing an invasive test is also used in the model after a positive or a 'no result' for NIPT in case of triage, or after a positive NIPT result in case of 1st line NIPT. In case of a 'no result' NIPT in first line we assume screening continues with the current approach. The total cost for an invasive procedure and genetic testing for Down syndrome is on average €934 based on the data of NIHDI.

The total number of invasive tests in Belgium in 2011 is 7586. Based on the modelling exercise, 4374 are performed following the current screening. Based on expert opinion and model calibration, the remaining tests are performed: (1) following a NT>3.5mm (n=398), (2) for other indications (but samples are also tested for T21) (n=1814), and (3) in pregnant women who want more certainty without being at increased risk (n=1000). These 1000 women represent 0.8% of all pregnant women and we assume no prior screening test is performed or billed. The number of 1000 primary invasive tests is included in all modelled scenarios of current screening and triage NIPT. However, we assume these 1000 women will opt for primary NIPT screening once available as NIPT provides more certainty. In Belgium, the samples obtained from invasive procedures are analyzed at one of the

eight centres for human genetics. The test sensitivity of chorionic villus sampling (CVS) has been found to be somewhat lower compared to amniocentesis (98.47% versus 99.32%, respectively).[12] However, in our model, we assume 100% accuracy for these last-stage analyses.

Invasive testing carries a risk of membrane rupture with amniotic fluid leakage.[13] This may lead in about 1% of procedures to a hospitalization of about one week at a cost of €3515 and in about 1% to a procedure-related miscarriage. The latter is based on a Cochrane review which states that "*the best estimate of an 'excess' risk after second trimester amniocentesis comes from Tabor 1986.[14] In a low-risk population with a background pregnancy loss of around 2%, a mid-trimester amniocentesis will increase this risk by another 1%*".[15] This miscarriage rate may be more frequent after CVS compared with amniocentesis, and rates are expectedly lower in experienced hands.[14] It has been reported that 89% to 97% of the women who received a positive diagnosis of T21 during the prenatal period had an induced abortion.[16] Belgian data covering a 10 year period (2003-2012) in a single centre show a diagnosis of T21 after an invasive test during pregnancy in 44 cases. The pregnancy was terminated in 42 out of these 44 cases (95.45%, 95%CI 87.7%–99.4%), which is used in the model. This is in agreement with a proportion of 94.8% (95% CI 92.5–96.5) reported in Paris[11] and 93.3% (250 out of 268) in the UK.[17] Pregnancy termination is associated with a 24-48 hour hospitalization and costs on average €914.

Uncertainty and scenario analyses

Both one-way and probabilistic sensitivity analyses were applied. The impact of uncertainty around all the model's input parameters on the results was modelled probabilistically. The applied distribution depends on the type of variable:[18] probabilities (e.g. NIPT test failure or procedure related foetal loss) and test characteristics (sensitivity and specificity) were modelled as beta distributions. This distribution is limited to the 0-1 scale and reflects the possible outcomes for these variables. For cost variables with less informative data for a stochastic distribution, uniform distributions were applied.

Several one-way scenario analyses are modelled:

- The cut-off risk of 1:300 for T21 is changed to 1:600, 1:1100, 1:1700, 1:2400, and 1:3000.
- A scenario with 90% NIPT uptake in first line (instead of the current uptake with 1st and 2nd trimester screening of about 80%) is presented without changing any other input variable.
- A threshold analysis is performed changing the price of NIPT to keep the short-term costs per case of T21 diagnosed at the same level as in the current screening scenario.
- A scenario with improved performance of the current screening (sensitivity of 77.5% instead of 72.5%)

For further details, we refer to the supplementary file. 1000 Latin Hypercube simulations are performed and correlation coefficients are calculated in a probabilistic sensitivity analysis. The @Risk add-on tool (Palisade Corporation) is used for probabilistic modelling and sensitivity analyses.

Table 1 – Input variables (volumes and probabilities)

Variable	Mean	Uncertainty	Source
Screening uptake	78.87%		Belgian data (NIHDI)
Testing uptake (i.e. screening + invasive test without prior screening)	79.74%	Scenario analysis: 90%	Belgian data (NIHDI)
Current screening accuracy		Scenario analysis +	Belgian data (AML)
Sensitivity	72.54%	Beta(103;39)	
Specificity	95.03%	Beta(117,144;6121)	
NIPT			Literature[10]
Sensitivity	99.3%	95%CI: 98.2-99.8% (Beta(6;1.06);2.5%:0.982;97.5%:0.998)	
Specificity	99.84%	95%CI: 99.69-99.92% (Beta(3;1.014);2.5%:0.9969;97.5%:0.9992)	
NIPT test failure rate			Expert opinion plus literature[10]
First test (at week 12)	4%	Min.-max: 3-7% (Beta(2;6);min:0.03;max:0.07)	
Second test (at week 13)	2%	Min.-max: 1-3% (Beta(2;2);min:0.01;max:0.03)	
Probability of having an invasive test (after a positive screening test or NIPT)	87.5%	Min.-max: 0.8-0.95% (Beta(2;2);min:0,8;max:0,95)	Assumption and model fitting plus literature[11]
Number of invasive tests without prior screening	3212	Conditional Beta distribution (313.9; 1000; 84.1; 1814)	Belgian NIHDI data and model fitting; literature[19]
Invasive testing (CVS or amniocentesis)		/	Considered as gold standard
Sensitivity	100%		
Specificity	100%		
Procedure related foetal loss after invasive test	1%	Min.-max: 0.5-2% (Beta(2;4);min:0.005;max:0.02)	Literature[14]
Hospitalization for amniotic fluid leakage after invasive test	1%	Min.-max: 0.5-2% (Beta(2;4);min:0.005;max:0.02)	Literature[13]
Pregnancy termination after T21 diagnosis	95.45%	Beta(42;2)	Belgian data and literature[11 17]
Spontaneous miscarriage			Literature[6 7]
Miscarriage all (p)	0.05, 0.025, 0.015 at week 10, 12, and 14, respectively.*		
T21 miscarriage (p)	0.36, 0.3, 0.25 at week 10, 12, and 14, respectively.		

AML: Algemeen Medisch Laboratorium bvba; CVS: chorionic villus sampling; NIHDI: National Institute for Health and Disability Insurance; NIPT: non-invasive prenatal test.
*Rounded numbers extracted from a published figure.[7]

Table 2 – Input variables (costs)

Variable	Mean	Uncertainty	Source
1st trimester screening	€80.42	/	NIHDI
2nd trimester screening	€45.03	/	NIHDI
NIPT	€460	Scenario and threshold analysis	University Hospital Leuven
Invasive diagnostic test	€934.21	Min.-max: €887.71; €980.71 (uniform)	NIHDI (and expert opinion for the distribution)
Hospitalization for leakage	€3514.54	+/- 20% (uniform)	NIHDI (and expert opinion for the distribution)
Pregnancy termination	€914.39	Min.-max: €658.24; €1170.54 (uniform)	NIHDI (and expert opinion for the distribution)

NIHDI: National Institute for Health and Disability Insurance; NIPT: non-invasive prenatal test. Exchange rate May 22, 2014: €1 = £0.81.

Results

Reference case

Table 3 presents the results for the three reference case scenarios. In the current screening situation without NIPT, 170 cases of T21 are diagnosed. 96 children with Down syndrome are born, of whom 41 after a false negative screening result. There are 58 iatrogenic miscarriages after T21-related invasive testing. Total short-term costs of screening are almost €15 million and the short-term average cost per T21 diagnosed is about €87,000.

Introducing NIPT as a triage test (cut-off 1:300) results in one extra case of T21 diagnosis missed after a false negative NIPT result. However, there are much less procedure-related miscarriages after T21-related invasive testing (16 versus 58). Both total short-term costs (minus €1.6 million) and short-term average cost per case of T21 diagnosed are lower.

Introducing NIPT in 1st line results in more cases of T21 diagnosed (n=215 versus currently 170), very few children with Down syndrome born after a false negative screening result (n=2 versus 41 currently), a significant decrease in iatrogenic miscarriages related to T21 (n=8 versus 58 currently). However, at a price of NIPT of €460, the short-term budget increases to almost €51 million with a tripled average cost per case of T21 diagnosed of about €236,000. The extra cost per extra case of T21 diagnosed versus NIPT as a triage test is about €840,000.

Table 3 – Results

Test strategy	Current screening	NIPT 2nd line	NIPT 1st line
(Down) births, diagnosis and miscarriages			
N° of births	122,543	122,554	122,560
N° of Down born	96	97	63
N° of Down born (false neg. screening)	41	42	2
N° of T21 detected	170	169	215
N° of proc.rel. miscarriages	76	34	26
N° of T21 proc.rel. misc.	58	16	8
Costs for testing during pregnancy			
1st & 2nd trim. screening cost	€7,252,215	€7,252,215	€89,123
NIPT cost	€0	€2,390,929	€47,969,932
Cost invasive tests	€7,086,886	€3,203,417	€2,435,450
Cost hosp.leakage & pregn.term.	€415,728	€268,375	€279,539
Total cost (Short term)	€14,754,829	€13,114,935	€50,774,045
Short term cost/T21 detected	€86,944	€77,696	€236,436
Extra cost per extra T21 detected	/	€2,738,197§	€839,936

Proc.rel.misc.: procedure-related miscarriage; § This result is located in the 3rd quadrant, i.e. fewer cases of T21 diagnosed with a lower cost. The results with their 95% credibility intervals (CrI) are not presented but are available upon request.

Uncertainty and scenario analyses

Figure 2 provides an overview of the most relevant scenarios, including the impact of uncertainty of all input variables. The x- and y-axis represent the number of T21 diagnoses and total short-term costs, respectively. We remark that these are not the only outcomes of importance. Other outcomes, such as the number of procedure-related miscarriages should also be taken into consideration. Further details on all outcomes are mentioned in supplementary tables.

More patients would receive NIPT in 2nd line if the risk cut-off after 1st and 2nd trimester screening is lowered. As a result, the number of T21 detections would increase and fewer children with Down syndrome would be born after a false negative screening. The number of procedure-related miscarriages would increase only slightly each time the cut-off risk is lowered. The short-term total screening costs and average cost per T21 detected are lower compared with the current screening situation if NIPT is used as triage test with a risk cut-off of up to 1:600. However, if the risk-cut off is lowered further the extra cost per extra T21 detected increases exponentially (Figure 2 and Table 6 in supplementary material).

The threshold analysis resulted in a price of about €152 which would keep the short-term screening cost per T21 diagnosed constant if NIPT is used in first line. This is illustrated in Figure 2. At this price and the current screening uptake of about 80%, we would do much better (more T21 detected, less children born with Down syndrome after false negative screening, and less procedure-related miscarriages). At a constant average cost of about €87,000 per case of T21 diagnosed this would lead to an increase in the short-term costs, proportional to the increased detection rate (see supplementary table). The same is shown in Figure 2 for a 90% uptake scenario.

Insert Figure 2 around here: 'Figure 2 – Presentation of most relevant screening scenarios'
See the discussion for further explanation on the interpretation of the line presenting the 'average cost per T21 detected (current screening)'. Remark: This figure does not present other outcomes of importance, such as the number of procedure-related miscarriages.

The probabilistic sensitivity analysis showed that the most important stochastic variables in the current screening model and the model with NIPT in 2nd line are the sensitivity of current screening and the probability of having an invasive test after positive screening.

Discussion

In Belgium, almost 100,000 women participate in current screening. Introducing NIPT as a contingent test or in 1st line is expected to reduce the number of procedure-related miscarriages. In addition, the number of T21 diagnoses missed by screening will be strongly reduced when NIPT is used in 1st line. Whereas NIPT as a contingent test at a price of €460 will lead to short-term savings of about €1.6 million, NIPT in 1st line has a high impact on budgets, unless the price of NIPT is considerably reduced.

Strengths and limitations of study

The major strength of the model is the availability of context-specific real-world information and the ability to reflect the current Belgian screening situation by calibrating the model to the number of women screened, the expected and observed number of children born with Down syndrome and the number of invasive tests performed in Belgium. This calibration ensures that the initial screening model, including a large amount of real-world Belgian data on test characteristics, probabilities and costs, reflects the current Belgian screening situation as accurately as possible. This initial model is then used to construct the 2nd and 1st line NIPT screening situation. The expected 219 births with Down syndrome if no screening is performed is used as a control variable and checked in all models and all simulations. Full details of the models are available in supplementary material.

When NIPT is compared with the current screening system, NIPT is clearly superior in terms of sensitivity and specificity for the detection of T21 and other types of trisomy. Nevertheless, the model focuses on the detection of T21 and does not take into account the effects of screening for trisomy 13 (T13) and 18 (T18). Among the aneuploidy forms, T21 has the highest birth prevalence rate.[20] Trisomy 18 occurs less frequently and T13 is rather rare and survival of neonates with T13 or T18 beyond the first days of life is rare.[21] The fetal fraction in T21 pregnancies is significantly higher compared with T13 and T18 pregnancies, which may help explain the higher sensitivity and specificity of NIPT for detecting T21.[22] More research is needed to evaluate the use of primary NIPT to detect trisomy 13 and 18 which may lead to more invasive tests because of false positive test results. If the current biochemical analyses are replaced by NIPT, the detection of some other chromosomal aberrations may be missed.[23] At present, the clinical importance is unclear as a NT>3.5mm will already pick up many of these abnormalities. This is of relevance, as keeping in place the biochemical screening in parallel with NIPT would lead to a much less pronounced drop in invasive testing with a different impact on both costs and effects of the NIPT scenarios modelled.

The major weakness of the model is the inability to apply a long-term horizon and translate outcomes to incremental cost-effectiveness ratios expressing results in euros per (quality-adjusted) life-year gained. Two studies incorporate a lifetime cost of Down syndrome from a societal perspective of $940,000[24] and $677,000,[25] respectively. A lifetime cost of Down syndrome of $900,000 is also mentioned by Cuckle et al.[26] This amount is extrapolated from a 1992 average lifetime societal costs for an individual with Down syndrome of $451,000.[27] The largest part (64%) was due to indirect costs (productivity losses) which were calculated with the human capital approach. However, in contrast to the friction cost approach, this over-estimates the total incremental cost for society. The friction-cost method, which is recommended by the Belgian guidelines for economic evaluations,[3] is based on the idea that organizations need a certain time span (the friction period) to restore the initial production level after an employee becomes absent from work. The amount of production lost to society will be much lower than the above stated numbers and depends on the length of this friction period.

Furthermore, quality of life is of major importance. One study included maternal QALYs in their analysis.[24] The QoL data used in this study were based on studies of Kuppermann et al.[28-30] in women seeking genetic counselling and being less than 20 weeks pregnant. Their preferences, based on a hypothetical situation, might be very different from parents having a child with Down syndrome. Both the impact on life years (as a result of procedure-related or induced miscarriage) and QoL (e.g. on parents during testing, people with/without Down syndrome and their parents) are not clear

enough to make proper calculations with a long-term horizon. Furthermore, as stated by Petrou,[31] *"the matter is complicated further when one considers the positive utility effects that might accrue from a future 'replacement' child. The important point to note, however, is that an objective economic evaluation that measures and values the resource savings that follow the abortion of the affected foetus or unborn child requires a commensurate measurement and valuation of averted benefits. Furthermore, this remains the case whenever averted costs are incorporated into the evaluation, since the foetus or unborn child is necessarily ascribed a future human status that, by any measure, will have positive value and utility."* There are also other relevant costs outside the health care system. *"When the resource use implications for other sectors of society are considered the issue becomes more complicated: for example, the avoided excess costs associated with educational and institutional care, would need to be considered, as well as the costs of voluntary services and care incurred by the family."*[32] Gathering the necessary information on all these incremental elements could be the subject of future research.

In an ideal situation, all of these incremental elements would be taken into account. However, a translation into (QA)LYs gained was not performed because, within the time frame of this study, not enough reliable data could be gathered to work this out. This does not mean that we consider longer term costs and effects unimportant. On the contrary, we present the impact on various outcomes such as T21 detection, procedure-related pregnancy loss and total number of Down births whether or not after a false negative screening test in a transparent way in order to inform our policy makers. Furthermore, if all harms (procedure-related pregnancy loss and Down birth after a false-negative screening result) are reduced and the cost per diagnosis stays the same, then it becomes difficult to oppose the introduction and reimbursement of this new technology.

Comparison with other studies

A systematic review of full economic evaluations on the cost-effectiveness of NIPT was performed in December 2013 by searching the websites of HTA institutes and the following databases: CRD HTA, CRD NHS EED, OVID Medline and Embase. Details on the search strategy and selection process are available elsewhere.[9] Seven full economic evaluations were retained.[24-26, 33-36] All studies were published recently (2011-2013). Five were performed in the US, one in Australia[34] and one in the UK.[26] An additional economic evaluation from Ontario, Canada, was published during the writing of this article.[19]

The comparator is different across the identified studies and results are as follows:

-   *Contingent screening with NIPT versus current practice*: Contingent screening is more efficient than current standard of care, providing benefits at a lower cost.[25, 33] In one of these studies, cost savings were obtained by including a cost for Down syndrome.[25] The only study without any explicit conflict of interest concludes that the introduction of NIPT for screening of high-risk pregnancies would result in better outcomes (additional T21 detected, reduced invasive testing and thus less procedure-related foetal losses), while costs would increase by about 10%, which will need further policy planning.[34]
-   *Contingent screening with NIPT versus universal NIPT screening*: Contingent screening is more efficient than universal screening.[26, 36] The cost for contingent screening is substantially lower than with universal screening.[36] Offering NIPT to all women would only become affordable if the NIPT costs fall substantially.[26]

- *Contingent screening with NIPT versus NIPT as a diagnostic tool*: Contingent screening with NIPT is more efficient than applying NIPT as a diagnostic tool.[24]

Results of the previous studies are unfortunately not easily transferable to the Belgian context for several reasons. The populations described in the economic evaluations differ. Some model the general population of pregnant women[26 36] while the other studies only include populations at high-risk for T21. Related to this, the interventions and comparators used in the models differ. Not all studies consider NIPT in both first and second line. Only two studies include universal NIPT screening,[26 36] of which one does not include the current situation.[36] Furthermore, the values for several input variables are often not representative for the Belgian situation. For example, the sensitivity of first trimester combined screening (85%) in the study of Song et al.[25], is much higher than in the real-world Belgian population. The focus of the economic evaluation lies in the first place on the number of T21 detected. However, when comparing the estimated number of children born with Down syndrome, one should be cautious about differences in e.g. pregnancy termination which is reported to be lower in e.g. the US compared with Europe.[37] As previously mentioned, inclusion of long-term costs and quality of life data should also be supported by better data.

The price of NIPT

The price of NIPT varies widely across the economic evaluations published in 2012 or 2013: $1200 (€880, £713),[33] $795 (€583, £472),[25] AU$743 (€479, £388),[34] and a price in the range of $500-$2000 (€367-€1466, £297-£1187).[26] The costs to perform this test are decreasing. In Belgium, the official price of the University Hospital in Leuven is €460 (£373). Sequenom has announced a low cost NIPT of $250 to $300 (€183-€220, £149-£178), to be available by the end of 2014.[38] These changes in prices, together with test accuracy, should be followed in order to take appropriate policy decisions.

Pressure for referral to NIPT

Most triage scenarios published as well as our model start from the combined ultrasound and biochemical screening. If reimbursement can be restricted to the 5% of the screened population using the 1:300 cut-off, this may actually lead to a reduction in overall harms and savings for the health care budget, even at a cost per NIPT of €460. However, in this case, there will be pressure both from physicians and patients, to further lower the threshold for referral to NIPT, officially or informally. Indeed, in the absence of rigid quality assessment, the ultrasound part of the current screening remains strongly operator (and machine) dependent. This may lead to an increase in the number of women considered at risk after the current screening and thus eligible for NIPT reimbursement.

Conditions for a successful introduction of NIPT

Providing correct information and counselling and respect for the decision taken by the women or parents remains a cornerstone of any screening process.

As mentioned above the NIPT test does not provide a result in a fraction of women tested. If primary NIPT is offered at gestational week 10 the proportion of 'no result' after a repeat NIPT may be 4% instead of 2%. If most of these women would opt directly for invasive testing instead of falling back to the current screening tests as we assumed, the reduction in harms related to the invasive procedure might not be realized. It is therefore crucial to monitor the performance of the real-life

implementation of NIPT not only for sensitivity and specificity, but also for the proportion of 'no results' and the uptake of invasive testing after a 'no result' answer for NIPT in first-line.

Several experts have expressed their fear that the quality of NT will decline once NIPT is broadly introduced. The ultrasound should remain a key component of the prenatal screening process also after the introduction of NIPT in second or first line. Women with a foetal NT>3.5 mm (the 99th percentile) are directly (without use of biochemistry information) offered genetic counselling, diagnostic invasive testing and follow-up in keeping with international guidelines.[19] In such cases, there is a greater than 30% risk of chromosomal abnormalities, including but not limited to T21,[17] and other abnormalities such as heart defects.[39 40]

It has repeatedly been recommended that NT based risk assessment should only be implemented in centres with appropriately trained and accredited sonographers using high-quality equipment. Results should be subject to regular audit by an external agency.[17 40] Such requirements are still to be implemented in Belgium. Also the calibration of the ultrasound machines seems to be a problem.[41] For example, an NT of 3.5mm is reported as 3.2mm on one machine and as 3.8mm on another instrument. This finding illustrates the clear need for further standardization of the NT assessment. We believe that improving the quality of the ultrasound NT assessment in Belgium could increase the overall sensitivity of the screening, e.g. from 72.5% to 77.5% at 95% specificity. This improvement has been modelled separately and confirms that any improvement of the current screening sensitivity is mainly of importance when NIPT is used in second line, reducing the number of T21 cases missed because of a false negative result. It could also help in the acceptance of the current screening as alternative test in cases where NIPT does not provide a result in first line screening. Amniocentesis and CVS carry a 1 to 2% risk of membrane rupture, a 0.3% risk of sustained oligohydramnios,[13] and a 1% risk of induced miscarriage, which may be higher after CVS as compared with amniocentesis.[14 42] It has been suggested that 100 to 400 CVSs are needed before the learning curve reaches a plateau.[42] The risk may thus be lower in the hands of experienced operators and higher in low–volume, less experienced centres. Currently, no required minimum volumes have been defined in Belgium and invasive testing is still performed in many small centres. Therefore we applied a 1% risk of procedure-related miscarriage after CVS or amniocentesis.

Conclusions and policy implications

In comparison with the current prenatal screening for trisomy 21, the appropriate use of NIPT in either first or second line clearly improves the benefit-risk ratio. Based on the availability of data, it was not possible to reliably calculate cost per (QA)LY gained. From an economic point of view, assuming that we accept the current screening situation, we recommend our National Health Insurer to cover the cost of NIPT if the introduction of NIPT does not increase the screening cost per case of trisomy 21 detected. If offered at the current price of €460, NIPT can be introduced as a triage test, even if the screening risk cut-off is lowered from 1:300 to 1:600, corresponding to about 9% positive screen results eligible for NIPT reimbursement. Attention should be paid to further increase the quality of current screening with NT. As the number of invasive diagnostic tests will likely decrease, procedures should be centralized. In terms of benefits and harms, the use of NIPT in first line is preferred over its use in second line. However, the cost of NIPT should be lowered to about €150 in order not to increase the screening cost per case of trisomy 21 detected. In Belgium, at this (future) price level, NIPT should be offered to and reimbursed for all pregnant women.

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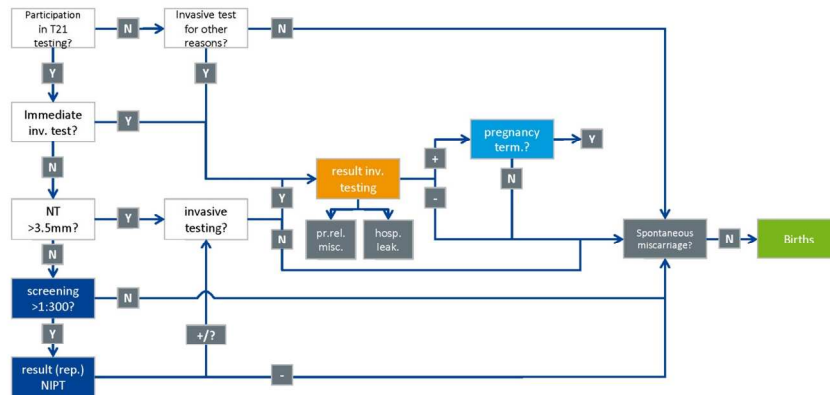
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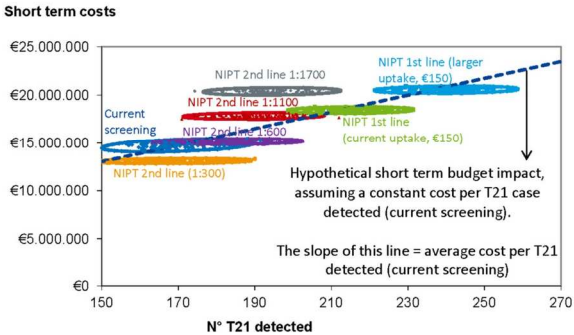
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Hosp.leak.: hospitalisation for leakage; inv.: invasive; pr.rel.misc.: procedure-related miscarriage; rep.: repeat; term.: termination.
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Short term costs

See the discussion for further explanation on the interpretation of the line presenting the 'average cost per T21 detected (current screening)'. Remark: This figure does not present other outcomes of importance, such as the number of procedure-related miscarriages.
139x197mm (300 x 300 DPI)

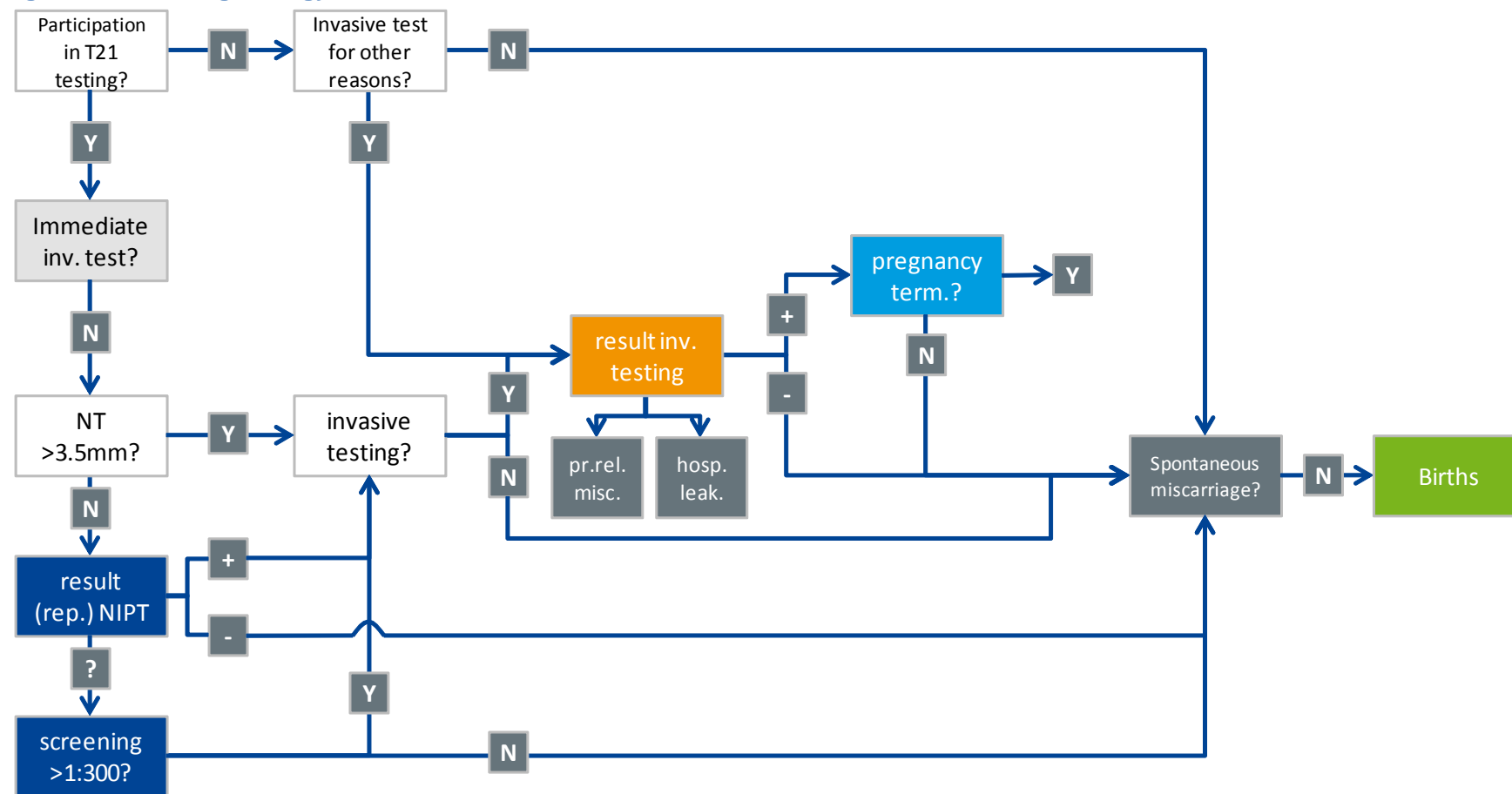## Supplementary material

Modelling of NIPT

Figure 3 presents an overview of the current screening strategy in Belgium. In Figure 4, the current first trimester biochemistry screening and second trimester screening is replaced by NIPT at week 12.

In the next part of this supplementary file, we present and explain the three models in detail (current screening, NIPT 2nd line and NIPT 1st line) with inclusion of the number of pregnant women and T21 pregnancies at different moments in the model.

Figure 3 – Current screening strategy

Hosp.leak.: hospitalization for leakage; inv.: invasive; pr.rel.misc.: procedure-related miscarriage; term.: termination.

Figure 4 – Screening strategy with NIPT as first-line test

Hosp.leak.: hospitalization for leakage; inv.: invasive; pr.rel.misc.: procedure-related miscarriage; rep.: repeat; term.: termination.

Supplementary material

In this part of the supplementary file we transparently present the three screening models: current screening, NIPT 2nd line, and NIPT 1st line. The figures of the models are copies from the original excel file, including exact numbers. These numbers represent (singleton) pregnancies and the number of T21 foetuses is added between brackets. All transitions are mentioned on the figures and explained with a short reference to the full text of the report.[9] Small differences in numbers (maximum 1 unit) might be possible due to the presentation of rounded numbers. In the original calculations, full details with non-rounded numbers were taken into account.

Current screening:

Part 1:

- **1** : 131567 pregnant women at week 10 including 350 T21 foetuses (part 2.1.3.4 and Table 9).

- **2** : Exclusion of 1.8% twin pregnancies (part 2.1.3.3 and Table 9). 129199 singleton pregnancies and 2368 twin pregnancies.

- **3** : Impact of miscarriage between week 10 and 40 (part 2.1.3.4 and Table 9). 2368 x (1-0.05) = 2250, 8 x (1-0.36) = 5.

- **4a** → **4e** : Impact of miscarriage between week 10 and 15 (part 2.1.3.4 and Table 9).

- **5a** , **5b** , **5c** : 1st and 2nd trimester screenings (part 2.1.6.1 and Table 12): number of tests, cost per activity, and % of screening uptake. E.g. 5a) 26 056/129 199 = 20.17%.

- **6a** , **6b** , **6c** : For simplicity, numbers are recalculated to week 14 and we assume that further steps are taken at week 14 (although in reality this might be between week 11 and 20). This has no meaningful impact on results since afterwards spontaneous pregnancy termination is modelled in one step between week 14 and 40.

- **6d** : The remaining pregnant women that did not participate in screening (124 608 – 21 560 – 51 583 – 25 130 = 26 335).

- **7a** , **7b** : Total number of singleton pregnant women (not) participating in screening. Number of T21 fetusses (292 in total) is mentioned between brackets.

- **8a** , **8b** : 398 pregnant women with an ultrasound detected NT>3.5mm are referred directly for invasive testing. They are divided proportionally among the screening (n=314) and no-screening (n=84) participants (see 2.1.6.3). It was assumed that women opting for an invasive test based on NT had an increased prevalence of a T21 pregnancy of 1:10.

Part 2:

- **9a**, **9b**: Exclusion of the high-risk pregnancies (NT>3.5mm): 26 335 – 84 = 26 251; 98 273 – 314 = 97 959.

- **10**, **10**: Results of the current screening. E.g. True negatives: (97 959 – 199) x specificity of 95.0343% = 92 906; True positives: 199 x sensitivity of 72.5352% = 144 (part 2.1.6.1).

- **11**, **11**: After a positive screening test result, we assume 87.5% of women choose to have an invasive diagnostic test (part 2.1.6.3). Thus (4855+144) x 87.5% = 4374.

- **12**: In Belgium, there was a total of 7586 of invasive tests (part 2.1.6.3). This leaves us with 3212 (7586 – 4374) invasive tests. We already identified 398 (314+84) pregnant women with an ultrasound detected NT>3.5mm. We assume another 1000 invasive tests for T21 detection are performed in pregnant women (often at low risk) who wish to have more certainty than can be provided with the current screening, and/or are referred based on age over 35 (despite existing guidelines). The remaining 1814 invasive tests are performed for non-T21 indications, including structural anomalies detected with ultrasound not related to T21 detection. The 1000 and 84 invasive tests are specifically for T21 and were not counted before and represent another 0.87% of the pregnant population. This slightly increase the overall uptake (of any type of) testing for Down from 78.87 to 79.74%.

- **13**, **13**: After CVS or amniocentesis, an incremental procedure related foetal loss of on average 1% was assumed in our model (e.g. 4374 x 1% = 44). We also included a 1% risk of hospitalization for one week for leakage. The costs for such a stay in an acute hospital in Belgium are €3515 (part 2.1.6.3).

- **14**: One of the outcomes in our model is the number of procedure related miscarriages and the number of such miscarriages related to T21 detection. The latter excludes the miscarriages related to the 1814 invasive tests performed for non-T21 indications.

- **15**: In the 'no screening uptake' group, there are 23 437 singleton pregnant women (26 251 – 1000 – 1814 = 23 437).

Part 3:

- **16**, **16**: In our model we assume the invasive diagnostic test is 100% sensitive and 100% specific (part 2.1.6.3). E.g. (4374 – 126) – (44 – 1.3) = 4205 and 126 – 1.3 = 125.

- **17**, **17**: T21 pregnancy termination was induced in 95.45% (part 2.1.6.4). E.g. 125 x 95.5% = 119

- **18** → **18**: Spontaneous miscarriage is taken into account (part 2.1.6.5, 2.1.3.4 and Table 9). E.g. 18a) (125 – 119) x 0.25 = 1.4; 4205 x 0.0144 + 1.4 = 62; 18c) 48 x 0.25 = 12; (23 437 – 48) x 0.0144 + 12 = 350.

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- **19** → **19** : The total number of singleton births at week 40 with the number of Down births between brackets. E.g. 19a) (4205 + 125) − (119 + 62) = 4149; 125 − (119 + 1.4) = 4.3; 19c) 23 437 − 350 = 23 087; 48 − 12 = 35.7.

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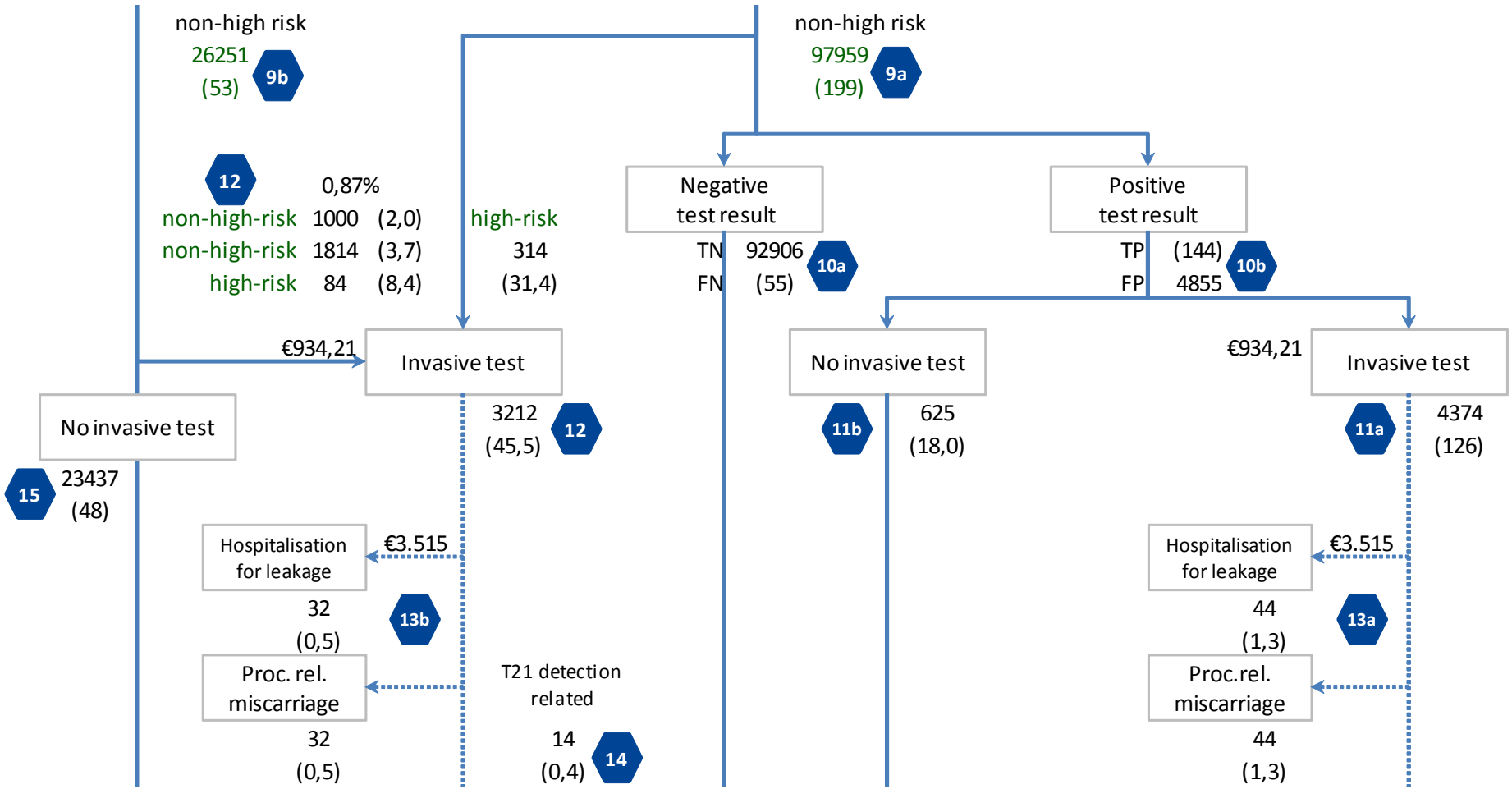6
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Part 1 (current screening)

Part 2 (current screening)

non-high risk

26251 **9b**
(53)

non-high risk

97959 **9a**
(199)

12   0,87%

non-high-risk   1000   (2,0)
non-high-risk   1814   (3,7)   high-risk
high-risk   84   (8,4)   314
                                    (31,4)

Negative
test result

TN   92906 **10a**
FN   (55)

Positive
test result

TP   (144) **10b**
FP   4855

€934,21   Invasive test   No invasive test   €934,21   Invasive test

                              3212 **12**   625   4374
No invasive test   (45,5)   (18,0)   (126)
                       11b   **11a**

23437
15 (48)

Hospitalisation   €3.515   Hospitalisation   €3.515
for leakage   for leakage

32   **13b**   44   **13a**
(0,5)   (1,3)

Proc. rel.   T21 detection   Proc. rel.
miscarriage   related   miscarriage

32   14   44
(0,5)   (0,4) **14**   (1,3)

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Part 3 (current screening)

NIPT 2nd line:

Part 1:

- **1** → **8b** : See current screening

Part 2:

- All blue hexagons: See current screening

- **11** : NIPT is offered to 4999 (4855+144) women at increased risk after current screening (part 2.1.4.2). We assume the first NIPT is repeated in 4% of cases. We assume the second NIPT test is performed about one week later and therefore also take into account the number of miscarriage during 1 week (4999 x 4% x (1 – (0.015 – 0.01)) = 199). Each NIPT test costs €460 (part 2.1.6.2).

- **11** , **11** , **11** : We assume that after repeat testing there is no result in 2% of cases: 11b) 4999 x 2% = 100; 144 x 2% = 3. For the remaining 98% the results of NIPT screening are calculated: E.g. True negatives: (4855 x specificity of 99.84%) x (98%) = 4750; True positives: (144 x sensitivity of 99.30%) x (98%) = 140 (part 2.1.6.2).

- **12** , **12** : After a positive NIPT screening test result or no NIPT result (but previously a positive test result after current screening), we assume 87.5% of women chooses to have an invasive diagnostic test (part 2.1.6.3). Thus (100 + 140 + 8) x 87.5% = 217.

- **13** : Same reasoning as for **13** (1% hospitalizations for leakage and 1% procedure related miscarriages) but with other underlying numbers as mentioned on the figure.

Part 3:

- All blue hexagons: See current screening

- **16** → **19** : Same reasoning as for **16** → **19** but with other underlying numbers as mentioned on the figure.

Part 2 (NIPT 2nd line)

non-high risk
26251 **9b**
(53)

non-high risk
97959 **9a**
(199)

Negative test result

Positive test result

TN 92906 **10a**
FN (55)

TP (144) **10b**
FP 4855

12 0,87%
non-high-risk 1000 (2,0)
non-high-risk 1814 (3,7)
high-risk 84 (8,4)

high-risk
314
(31,4)

11 repeat

€460,00 NIPT (1st and repeat) 199

€934,21 Invasive test

Negative test result

No test result

Positive test result

3212 **12**
(45,5)

TN 4750 **11a**
FN (1,0)

100 **11b**
(3)

TP (140) **11c**
FP 8

No invasive test

23437 **15**
(48)

No invasive test

€934,21 Invasive test

Hospitalisation for leakage
32
(0,5)

13b

31 **12b**
(17,9)

217 **12a**
(125)

Hospitalisation for leakage
2
(1,3)

€3.515

€3.515

13a

Proc. rel. Miscarriage
32
(0,5)

T21 detection related
14 **14**
(0,4)

Proc. rel. Miscarriage
2
(1,3)

Part 3 (NIPT 2nd line)

TP (Down) — 16b — TN

(45,1)　　　3135

€914 → Pregnancy termination — 17b — 43,0 (43,0)

Spontaneous Miscarriage — 18b — 46 (0,5)

Spontaneous Miscarriage — 18c — 350 (11,9)

N° of births (with Down) — 19c — 23087 (35,7)

N° of births (with Down) — 19b — 3091 (1,5)

No further tests — 11a + 12b — 4782 (18,9)

1356 (14)　Spontaneous Miscarriage　74 (4,7) — 18d / 18e

N° of births (with Down) — 19d — 91604 (41,0)

N° of births (with Down) — 19e — 4677 (14,2)

TP (Down) — 16a — TN

(124)　　　91

€914 → Pregnancy termination — 17a — 118 (118)

Spontaneous Miscarriage — 18a — 3 (1,4)

N° of births (with Down) — 19a — 94 (4,2)

NIPT 1st line:

Part 1:

- All blue hexagons: See current screening
- **(5a)**, **(5b)**, **(5c)** : The current first and second trimester screening is replaced by NIPT and we assume the NIPT is performed at week 12 (part 2.1.4.3). Taking into account the number of spontaneous miscarriages, recalculating 98,273 singleton pregnant women from week 14 to 12 results in 99,281 pregnant women. Furthermore, we assume that the 1000 women who are directly referred to invasive testing based on age (despite existing guidelines) or the wish to have more certainty than can be provided with the current testing, will now opt to have a NIPT test. Recalculating from week 14 to 12, this results in 1010 extra NIPT tests.
- **(6)** : One week later, 3991 repeat tests are performed (98,774 + 1005) x 4% = 3991.

Part 2:

- All blue hexagons: See current screening.
- **(5)** : see **(5a)** in part 1.
- **(9a)** : The 314 pregnant women with an ultrasound detected NT>3.5mm continue to be referred directly for invasive testing (part 2.1.4.3). The 1000 extra NIPT tests are taken into account, thus 98 273 – 314 + 1000 = 98 959.
- **(10)**, **(10)**, **(10)** : We assume that after repeat testing there is no result in 2% of cases: 10b) 98 959 x 2% = 1979; 201 x 2% = 4. For the remaining 98% the results of NIPT screening are calculated: E.g. True negatives: ((98 959 – 201) x specificity of 99.84%) x (98%) = 96 628; True positives: (201 x sensitivity of 99.30%) x (98%) = 196 (part 2.1.6.2).
- **(11)** : In case no NIPT result is obtained after a repeat NIPT the current screening strategy is applied (part 2.1.4.3).
- **(11)**, **(11)** : Results of the current screening. E.g. True negatives: (1979 – 4) x specificity of 95.0343% = 1877; True positives: 4 x sensitivity of 72.5352% = 2.9 (part 2.1.6.1).
- **(12)**, **(12)** : After a positive NIPT screening test result or a positive current screening test result (after a NIPT no result), we assume 87.5% of women chooses to have an invasive diagnostic test (part 2.1.6.3). Thus (196 + 155 + 2.9 + 98) x 87.5% = 395.
- **(12)** : The number of invasive tests in the 'no screening uptake' arm is 2212 instead of 3212 (excluding those 1000 pregnant women: see point 5).
- **(13)** → **(14)** : Same reasoning as for **(13)** → **(14)** but with other underlying numbers as mentioned on the figure.

Part 3:

- All blue hexagons: See current screening.

- ⬡16 → ⬡19f : Same reasoning as for ⬡16 → ⬡19 but with other underlying numbers as mentioned on the figure.

Part 1 (NIPT 1st line)

women who are 10 weeks pregnant

1,80%

1 131567 (350)

women who are 10 weeks pregnant (singletons)

2 week 10 twin pregnancies

129199 (342)

2368 (8)

women who are 11 weeks pregnant (singletons)

2331 (7)

4a 127191 (327)

5c 1010

1st NIPT

99281

€460,00

women who are 12 weeks pregnant (singletons)

4b 125886 (313)

2307 (7)

w12   26605

5b 1005

6 3991

€460,00

repeat NIPT

98774

women who are 13 weeks pregnant (singletons)

4c 125244 (300)

2296 (7)

w13   26470

extra

5a 1000

98273

women who are 14 weeks pregnant (singletons)

4d 124608 (292)

2284 (7)

w14   26335

women who are 15 weeks pregnant (singletons)

4e 123979 (284)

week 15 twin pregnancies

2273 (6)

No screening uptake (w14)

Screening uptake (w14)

week 40 N° of twin births

high-risk   total

high-risk   total

3 2250 (5)

8b 84 (8)

7b 26335 (62)

8a 314 (31)

7a 98273 (230)

Part 2 (NIPT 1st line)

non-high risk

26251 **9b**

(53)

5

non-high-risk 1000 (2,0)
non-high-risk 1814 (3,7)
high-risk 84 (8,4)

high-risk

314

(31,4)

€934,21

Invasive test

2212 **12c**

(43,5)

No invasive test

15 23437

(48)

Hospitalisation
for leakage €3.515

22 **13b**

(0,4)

Proc. rel.
Miscarriage

22

(0,4)

T21 detection
related

4 **14**

(0,4)

non-high risk

98959 **9a**

(201)

Negative test result	No test result	Positive test result
TN 96628 **10a**	1979 **10b**	TP (196) **10c**
FN (1,4)	(4)	FP 155

€45,03

11 Current screening

Negative test result	Positive test result
TN 1877 **11a**	TP (2,9) **11b**
FN (1,1)	FP 98

No invasive test

56 **12b**

(24,8)

€934,21 Invasive test

395 **12a**

(174)

Hospitalisation
for leakage €3.515

4 **13a**

(1,7)

Proc. rel.
Miscarriage

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(1,7)

Part 3 (NIPT 1st line)

TP (Down)	16b	TN	
(43,0)		2147	

€914 → Pregnancy termination
17b — 41,1 (41,1)

Spontaneous Miscarriage
18b — 32 (0,5)

Spontaneous Miscarriage
350 — 18c (11,9)

1396 (0,3) → Spontaneous Miscarriage
18d

27 (0,3) → Spontaneous Miscarriage
18e

Spontaneous Miscarriage
6,7 (6,2)
18f

TP (Down) — 16a — TN
(172) — 219

€914 → Pregnancy termination
17a — 164 (164)

Spontaneous Miscarriage
18a — 5 (2,0)

N° of births (with Down)
19c — 23087 (35,7)

N° of births (with Down)
19b — 2117 (1,5)

N° of births (with Down)
19d — 95233 (1,0)

N° of births (with Down)
19e — 1851 (0,8)

N° of births (with Down)
19f — 50 (18,6)

N° of births (with Down)
19a — 222 (5,9)

Supplementary material

Scenario analyses

Several scenario analyses are modelled:

- In Belgium, the overall uptake (of any type of) testing for Down is currently about 80%. If NIPT would be offered in first line, there is a possibility that the screening uptake of primary NIPT will be higher than for the current screening. A large survey in the UK suggests an uptake of primary NIPT of 88.2% (972/1103; 95%CI 86.1–90%), including respondents who would currently decline T21 screening.[43] A scenario with 90% NIPT uptake in first line is presented without changing any other input variable (see Table 4).
- In the reference case, the price of NIPT is set at €460. If NIPT would be used in 1st line, the eligible population would be much larger and scale effects could result in lower prices. Also evolution in technology will help. A threshold analysis is performed, changing the price of NIPT to keep the short-term costs per case of T21 detected at the same level as in the current screening scenario. This price was about €150. Results with this lower price are presented in Figure 2 and Table 4.
- In the reference case, a cut-off risk of 1:300 for T21 is used. Based on Belgian context-specific data, this results in a referral of about 5% of all pregnant women for definitive prenatal diagnosis using an invasive test, while the sensitivity is 72.5% (AML data). Lowering of the threshold is considered in the NIPT triage scenario. The cut-off risk with specificity closest to 95% (1:300), 90% (1:600), 85% (1:1100), 80% (1:1700) and 75% (1:2400) were selected plus the lowest reported cut-off risk of 1:3000 which has a specificity of 71%. Sensitivity and specificity are modelled with beta distributions reflecting the parameters from the AML data (see Table 5). Results are presented in Table 6.
- In Belgium, based on expert opinion, the sensitivity of the current screening could be improved by increasing the quality of the current screening, especially the quality of the nuchal translucency measure. An absolute increase of 5% in the current screening sensitivity was applied to model this, i.e. being 77.5% instead of 72.5%, without changing specificity. These results are also presented in Table 6.

Table 4 – Changing the uptake and price of NIPT

	Test strategy Uptake	NIPT 1st line 80%	NIPT 1st line 90%	NIPT 1st line 80%	NIPT 1st line 90%
	NIPT price	€460	€460	€150	€150
(Down) births, diagnosis and miscarriages					
N° of births		122,560	122,542	122,560	122,542
N° of Down born		63	45	63	45
N° of Down born (false neg. screening)		2	2	2	2
N° of T21 detected		215	240	215	240
N° of proc.rel. miscarriages		26	27	26	27
N° of T21 proc.rel. misc.		8	8	8	8
Costs for testing during pregnancy					
1st & 2nd trim. screening cost		€89,123	€100,718	€89,123	€100,718
NIPT cost		€47,969,932	€54,191,054	€15,642,369	€17,670,996
Cost invasive tests		€2,435,450	€2,486,456	€2,435,450	€2,486,456
Cost hosp.leakage & pregn.term.		€279,539	€303,308	€279,539	€303,308
Total cost (Short term)		**€50,774,045**	**€57,081,536**	**€18,446,482**	**€20,561,478**
Short term cost/T21 detected		**€236,436**	**€238,113**	**€85,897**	**€85,769**
Extra cost per extra T21 detected§		€839,936	€626,914	€118,870	€106,160

Proc.rel. misc.: procedure-related miscarriage; § The extra cost per extra case of T21 diagnosed was compared with NIPT 2nd line (i.e. the previous best alternative) but with a price of €460 for NIPT (we assume such a lower price would in first instance only be probable with high volumes of NIPT such as in 1st line).

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Table 5 – sensitivity and specificity of 1st and 2nd trimester screening related to the cut-off risk

Cut-off risk	Sensitivity	Uncertainty	Specificity	Uncertainty
1:300	72.54%	Beta(103;39)	95.03%	Beta(117 144; 6121)
1:600	80.99%	Beta(115;27)	90.88%	Beta(112 018; 11 247)
1:1100	84.51%	Beta(120;22)	85.41%	Beta(105 283; 17 982)
1:1700	87.32%	Beta(124;18)	80.17%	Beta(98 817; 24 448)
1:2400	87.32%	Beta(124;18)	75.18%	Beta(92 675; 30 590)
1:3000	88.73%	Beta(126;16)	71.46%	Beta(88 087; 35 178)

Source: AML data

Table 6 – Varying the sensitivity of the current screening approach or risk cut-off if NIPT is used in 2nd line

Test strategy	Current screening	NIPT 2nd line + 77.5% sensitivity*	NIPT 2nd line (1/300)	NIPT 2nd line (1/600)	NIPT 2nd line (1/1100)	NIPT 2nd line (1/1700)	NIPT 2nd line (1/2400)	NIPT 2nd line (1/3000)
(Down) births, diagnosis and miscarriages								
N° of births	122,543	122,546	122,554	122,529	122,509	122,490	122,476	122,463
N° of Down born	96	90	97	86	82	78	78	77
N° of Down born (false neg. screening)	41	34	42	29	24	20	20	18
N° of T21 detected	170	178	169	184	190	194	194	197
N° of proc.rel. miscarriages	76	34	34	35	36	37	38	39
N° of T21 proc.rel. misc.	58	16	16	17	18	19	20	21
Costs for testing during pregnancy								
1st & 2nd trim. screening cost	€7,252,215	€7,252,215	€7,252,215	€7,252,215	€7,252,215	€7,252,215	€7,252,215	€7,252,215
NIPT cost	€0	€2,395,686	€2,390,929	€4,343,507	€6,901,721	€9,357,267	€11,687,078	€13,428,890
Cost invasive tests	€7,086,886	€3,211,490	€3,203,417	€3,288,763	€3,388,650	€3,483,651	€3,569,545	€3,636,013
Cost hosp.leakage & pregn.term.	€415,728	€276,151	€268,375	€284,228	€293,214	€301,016	€304,292	€308,923
Total cost (Short term)	**€14,754,829**	**€13,135,542**	**€13,114,935**	**€15,168,714**	**€17,835,800**	**€20,394,149**	**€22,813,130**	**€24,626,040**
Short term cost/T21 detected	**€86,944**	**€74,063**	**€77,696**	**€82,746**	**€94,188**	**€105,016**	**€117,474**	**€125,249**
Extra cost per extra T21 detected§	/	/	/§§	€142,110	€442,346	€531,269	/§§§	€1,750,512

*Proc.rel. misc.: procedure-related miscarriage; * In this scenario, we assume NIPT is used in 2nd line after current screening (1/300) but with an improved sensitivity of 77.5% instead of 72.5%. § This is calculated in a deterministic way since the simulations fall into different quadrants making the average of all simulations unreliable. §§ This is the initial comparator, thus no extra cost per extra T21 detected is calculated. §§§ Due to the same sensitivity and a lower specificity in comparison with the previous situation (based on the data of AML), this scenario is an example of extended dominance.*

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Introducing the non-invasive prenatal test for trisomy 21 in Belgium: a cost-consequences analysis

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Abstract

Background: First and second trimester screening for trisomy 21 (T21) is reimbursed for all pregnant women in Belgium. Using a cut-off risk of 1:300 for T21, about 5% of all pregnant women are referred for definitive prenatal diagnosis using an invasive test, at a sensitivity of (only) 72.5%. Sensitivity and specificity of the non-invasive prenatal test (NIPT) are over 99% but comes at a cost of €460 (£373) per test. The objective is to estimate the consequences of introducing NIPT for the detection of T21.

Methods: A cost-consequences analysis was performed presenting the impact on benefits, harms and costs. Context-specific real-world information was available to set up a model reflecting the current screening situation in Belgium. This model was used to construct the 2nd and 1st line NIPT screening scenarios applying information from the literature on NIPT's test accuracy.

Results: Introducing NIPT in 1st and 2nd line reduces harms by decreasing the number of procedure-related miscarriages after invasive testing. Offering NIPT in 1st line additionally will miss fewer cases of T21 due to less false negative test results. The introduction of NIPT in 2nd line results in cost savings which is not true for NIPT at current price in 1st line. If NIPT is offered to all pregnant women, the price should be lowered to about €150 to keep the screening cost per T21 diagnosis constant.

Conclusions: In Belgium, introduction and reimbursement of NIPT as 2nd line triage test significantly reduces procedure-related miscarriages without increasing short-term screening costs. Offering and reimbursing NIPT in 1st line to all pregnant women is preferred in the long-term, as it would in addition miss fewer cases of T21. However, taking into account the governmental limited resources for universal reimbursement, the price of NIPT should first be lowered substantially before this can be realized.

Strengths and limitations of this study

- The major strength of the model is the availability of context-specific real-world information and the ability to reflect the current Belgian screening situation by calibrating the model to the number of women screened, the expected and observed number of children born with Down syndrome and the number of invasive tests performed in Belgium. This calibration assures that the initial screening model reflects the current Belgian screening situation as ~~good~~ well as possible.

- The most important limitation of our analysis is, due to a lack of reliable data, the inability to apply a long-term horizon and translate outcomes to incremental cost-effectiveness ratios expressing results in euros per (quality-adjusted) life-year gained. However, by presenting the consequences of screening in a transparent way (which includes both the detection of T21, the number of Down births whether or not after a false negative screening test, and the number of procedure-related losses), we try to inform ~~the~~ policy makers in a transparent way about the possible consequences of introducing NIPT in different settings.

- In order to avoid a "black box" and to provide other researchers <u>with</u> the possibility to use and adopt the model to their context, details of the full model are included in supplementary files with a step by step explanation for every transition.

Introduction

Prenatal diagnosis of Down syndrome allows for informed decision making with regard to pregnancy continuation or termination. Multiple prenatal trisomy 21 (T21, Down syndrome)/aneuploidy screening strategies in the first and second trimester have been developed.[1] The most commonly used approach for first trimester screening in Belgium is the combination of the nuchal translucency (NT) ultrasound measure at week 12 (week 11-14), the level of free-beta-hCG (human chorionic gonadotrophin hormone) and PAPP-A (pregnancy associated plasma protein-A), in combination with age and medical history. The T21 screening in Belgium is fully reimbursed for all pregnant women and has a high uptake of nearly 80%. However, the overall sensitivity is rather low (~72.5%) compared with reports from neighbouring countries. This moderate performance is likely related to the absence of an obligatory quality assurance system for the nuchal translucency assessment in Belgium.

The non-invasive prenatal testing (NIPT) is performed on a blood sample of the pregnant woman containing circulating cell free DNA both from the mother and the placenta, which in nearly all cases is representative for the foetal DNA. NIPT has been shown to be highly accurate in the detection of common foetal autosomal trisomies, especially T21.[1] However, about 4% of the tests will not provide a result (reduced by half after repeated sampling). The 'no result' NIPT is often caused by a low proportion of foetal DNA, as seen when the sample is obtained before gestational week 12 or in obese women. In dizygotic twin pregnancies NIPT also remains a challenge. Because of its high cost NIPT was originally positioned as a triage test in pregnancies referred for invasive testing (chorionic villus sampling (CVS) or amniocentesis) because of a calculated risk, e.g. above 1:300. NIPT for primary screening (at week 12) of pregnant women with a NT under 3.5mm is becoming a real possibility in view of the growing number of validation studies in low risk pregnancies[2] and especially the prospect of a lower cost per test.

As part of its government-approved work programme, the Belgian Health Care Knowledge Centre (KCE) performed an economic evaluation of introducing NIPT in prenatal diagnosis of Down syndrome. The research questions were the following: 1) What is the impact of introducing NIPT on the benefits and harms of screening for trisomy 21 in the Belgian context? Benefits can be expressed in terms of detection of trisomy 21 such that informed decision making is possible. Possible harms in the process include membrane rupture with amniotic fluid leakage or miscarriage after an invasive test, and the risk of missing the detection of Down syndrome because of a false negative test result. 2) What is the impact on costs and budget for the health insurance of introducing NIPT? What is the cost for the detection of a case of trisomy 21 after introducing NIPT?

Methods

A time-dependent multi-stage transition probability model was developed in Excel in order to assess the consequences of introducing NIPT. This model allows following pregnant women during the screening process and pregnancy up to birth, taking into account e.g. spontaneous miscarriage rates. In accordance with the Belgian guidelines for economic evaluations,[3] the analysis includes direct health care costs from the perspective of the health care payer. Payments out of the public health care budget as well as patients' co-payments are included.

A short-term time horizon was applied in which costs and effects before birth were considered. Due to this short-term horizon, no discount rate was applied. A long-term horizon translating results in extra costs per (quality-adjusted) life year ((QA)LY) gained was not modelled due to a lack of reliable data and thus the hypothetical character of this scenario. In this cost-consequences analysis, the following outcomes were calculated: total number of live births and number of children born with Down syndrome, cases of T21 diagnosed during pregnancy, children with Down syndrome born after a false-negative screening result, procedure-related miscarriages (related to T21 detection), short-term screening cost, short-term screening cost per case of T21 diagnosed, and incremental cost per extra case of T21 diagnosed.

Population

The model includes all pregnancies in the Belgian population, except for twin pregnancies. These represent 1.8% of pregnancies and correspond to about 2.1% of all T21 cases.[4 5] Complete and up to date data from Flanders, the northern community of Belgium representing 54% of the children born in Belgium, were extrapolated to the Belgian situation. The model takes into account the different probabilities of a spontaneous loss of the foetus, for T21 and non-T21 pregnancies, adjusted for gestational week (e.g. 5% and 36% at week 10 for all and T21-pregnancies, respectively (see Table 1)).[6 7] A total of 122,739 births in Belgium in 2012 thus corresponds to 129,199 singleton pregnancies at gestational week 10. The observed live birth prevalence of Down syndrome in Belgium, extrapolated from the Flanders registry, was estimated at 98 in 2012, of which 96 after singleton pregnancies. Based on the age distribution of the pregnant women in Flanders and reported age related prevalence of Down syndrome,[8] 219 T21 singleton live births would be expected without screening, corresponding to 342 pregnancies at week 10. These numbers of expected and observed births of children with Down syndrome were used to calibrate the model.[9]

Comparators

The current practice in Belgium for first- and second trimester screening for T21 is modelled and serves as the initial comparator. NIPT is the intervention under consideration and is considered both as a contingent test (i.e. as triage or 2nd line test) and for primary screening (i.e. as 1st line test). Figure 1 presents the triage scenario in which NIPT is offered only to women at increased risk (>1:300) after current screening. The risk cut-off is changed in modelled scenario analyses (see part 'Uncertainty and scenario analyses'). The figures representing the current Belgian screening strategy and NIPT in 1st and 2nd line are presented as supplementary material.

Input variables

The values and probabilities of all input variables in the models are provided in Table 1. Costs for screening, adverse events and pregnancy termination are included and are expressed in € for the year 2013 (Table 2). These costs are based on data from our National Institute for Health and Disability Insurance (NIHDI).

Based on reimbursement data from NIHDI for the year 2011, excluding the 1.8% twin pregnancies, 78,168 pregnant women participate in first trimester screening (€80.42 per activity) and another 21,451 in second trimester screening (€45.03 per activity). The fee for these activities is exclusive of the ultrasound but includes the counselling which is performed by the health care worker offering antenatal screening. NIPT is no replacement of the ultrasound screening and thus no incremental impact on ultrasound screening is included in the model. After adjustments for gestational week, the

total screening uptake is estimated at 78.87%. If we also assume 1000 women ~~that~~who immediately undergo invasive testing for T21, the overall uptake of any type of testing for Down syndrome increases to 79.74%. In the reference case, this screening uptake is kept constant.

Sensitivity and specificity of screening at different risk cut-offs are based on the receiver operator characteristics (ROC) curve data from AML (Algemeen Medisch Laboratorium bvba), a large laboratory covering 40% of the first and second trimester screenings for Down syndrome in Flanders. In the reference case, a risk cut-off level of 1:300 is applied, which results in a sensitivity of 72.54% (95%CI: 0.649 – 0.795) and specificity of 95.03% (95%CI: 0.949 – 0.952). This is varied in modelled scenario analyses (see part 'Uncertainty and scenario analyses'~~further~~).

The baseline cost for NIPT (and also for a repeat NIPT if needed) is set at €460, i.e. the current price charged by the ~~u~~University ~~h~~Hospital of Leuven in Belgium. We assume a no first time NIPT result in 4% (3-7%) of cases, reduced to 2% (1-3%) after a repeat NIPT. These estimates are in agreement with 11 studies reviewed by Benn et al.[10] In the primary NIPT model we assume these 2% of women tested will accept to fall back on the current screening and not opt directly for an invasive test. Based on an overview of existing evidence, the sensitivity and specificity of NIPT tests with a result is assumed to be 99.3% (95%CI: 98.2-99.8%) and 99.84% (95%CI: 99.69-99.92%), respectively.[10] No additional cost for NIPT counselling is included since it is assumed that this would happen in a similar way as in the current screening approach and thus does not occur ~~to be~~as an incremental cost.

Invasive diagnostic testing is recommended after a positive current screening test or NIPT result in order to confirm the results. The proportion of women undergoing an invasive test after a positive screening was 86.9% (95%CI: 83.9~~ to ~~-89.5%) in a large study in Paris.[11] We use a similar probability of 87.5% (80-95%) which was obtained after model calibration. Having no real-world data at our disposal, this proportion of women undergoing an invasive test is also used in the model after a positive or a 'no result' for NIPT in case of triage, or after a positive NIPT result in case of ~~first ~~1st line NIPT. In case of a 'no result' NIPT in first line we assume screening continues with the current approach. The total cost for an invasive procedure and genetic testing for Down syndrome is on average €934 based on the data of NIHDI.

The total number of invasive tests in Belgium in 2011 is 7586. Based on the modelling exercise, 4374 are performed following the current screening. Based on expert opinion and model calibration, the remaining tests are performed: (1) following a NT>3.5mm (n=398), (2) for other indications (but samples are also tested for T21) (n=1814), and (3) in pregnant women who want more certainty without being at increased risk (n=1000). These 1000 women represent 0.8% of all pregnant women and we assume no prior screening test is performed or billed. The number of 1000 primary invasive tests is included in all modelled scenarios of current screening and triage NIPT. However, we assume these 1000 women will opt for primary NIPT screening once available as NIPT provides more certainty. In Belgium, the samples obtained from invasive procedures are analyzed at one of the eight centres for human genetics. The test sensitivity of chorionic villus sampling (CVS) has been found to be somewhat lower compared to amniocentesis (98.47% versus 99.32%, respectively).[12] However, in our model, we assume 100% accuracy for these last-stage analyses.

Invasive testing carries a risk of membrane rupture with amniotic fluid leakage.[13] This may lead in about 1% of procedures to a hospitali~~z~~sation of about one week at a cost of €3515 and in about 1% to a procedure-related miscarriage. The latter is based on a Cochrane review which states that "*the*

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best estimate of an 'excess' risk after second trimester amniocentesis comes from Tabor 1986.[14] In a low-risk population with a background pregnancy loss of around 2%, a mid-trimester amniocentesis will increase this risk by another 1%".[15] This miscarriage rate may be more frequent after CVS compared with amniocentesis, and rates are expectedly lower~~may be less frequent~~ in experienced hands.[14] It has been reported that 89% to 97% of the women who received a positive diagnosis of T21 during the prenatal period had an induced abortion.[16] Belgian data covering a 10 year period (2003-2012) in a single centre show a diagnosis of T21 after an invasive test during pregnancy in 44 cases. The pregnancy was terminated in 42 out of these 44 cases (95.45%, 95%CI 87.7%~~—~~–99.4%), which is used in the model. This is in agreement with a proportion of 94.8% (95% CI 92.5–96.5) reported in Paris[11] and 93.3% (250 out of 268) in the UK.[17] Pregnancy termination is associated with a 24-48 hour hospitalization and costs on average €914.

Uncertainty and scenario analyses

Both one-way and probabilistic sensitivity analyses were applied. The impact of uncertainty around all the model's input parameters on the results was modelled probabilistically. The applied distribution depends on the type of variable:[18] probabilities (e.g. NIPT test failure or procedure related foetal loss) and test characteristics (sensitivity and specificity) were modelled as beta distributions. This distribution is limited to the 0-1 scale and reflects the possible outcomes for these variables. For cost variables with less informative data for a stochastic distribution, uniform distributions were applied.

Several one-way scenario analyses are modelled:

- The cut-off risk of 1:300 for T21 is changed to 1:600, 1:1100, 1:1700, 1:2400, and 1:3000.
- A scenario with 90% NIPT uptake in first line (instead of the current uptake with 1st and 2nd trimester screening of about 80%) is presented without changing any other input variable.
- A threshold analysis is performed changing the price of NIPT to keep the short-term costs per case of T21 diagnosed at the same level as in the current screening scenario.
- A scenario with improved performance of the current screening (sensitivity of 77.5% instead of 72.5%)

For further details, we refer to the supplementary file. 1000 Latin Hypercube simulations are performed and correlation coefficients are calculated in a probabilistic sensitivity analysis. The @Risk add-on tool (Palisade Corporation) is used for probabilistic modelling and sensitivity analyses.

Table 1 – Input variables (volumes and probabilities)

Variable	Mean	Uncertainty	Source
Screening uptake	78.87%		Belgian data (NIHDI)
Testing uptake (i.e. screening + invasive test without prior screening)	79.74%	Scenario analysis: 90%	Belgian data (NIHDI)
Current screening accuracy		Scenario analysis +	Belgian data (AML)
Sensitivity	72.54%	Beta(103;39)	
Specificity	95.03%	Beta(117-,144;6121)	
NIPT			Literature[10]
Sensitivity	99.3%	95%CI: 98.2-99.8% (Beta(6;1.06);2.5%:0.982;97.5%:0.998)	
Specificity	99.84%	95%CI: 99.69-99.92% (Beta(3;1.014);2.5%:0.9969;97.5%:0.9992)	
NIPT test failure rate			Expert opinion plus literature[10]
First test (at week 12)	4%	Min.-max: 3-7% (Beta(2;6);min:0.03;max:0.07)	
Second test (at week 13)	2%	Min.-max: 1-3% (Beta(2;2);min:0.01;max:0.03)	
Probability of having an invasive test (after a positive screening test or NIPT)	87.5%	Min.-max: 0.8-0.95% (Beta(2;2);min:0,8;max:0,95)	Assumption and model fitting plus literature[11]
Number of invasive tests without prior screening	3212	Conditional Beta distribution (313.9; 1000; 84.1; 1814)	Belgian NIHDI data and model fitting; literature[19]
Invasive testing (CVS or amniocentesis)		/	Considered as gold standard
Sensitivity	100%		
Specificity	100%		
Procedure related foetal loss after invasive test	1%	Min.-max: 0.5-2% (Beta(2;4);min:0.005;max:0.02)	Literature[14]
Hospitalization for amniotic fluid leakage after invasive test	1%	Min.-max: 0.5-2% (Beta(2;4);min:0.005;max:0.02)	Literature[13]
Pregnancy termination after T21 diagnosis	95.45%	Beta(42;2)	Belgian data and literature[11 17]
Spontaneous miscarriage			Literature[6 7]
Miscarriage all (p)		0.05, 0.025, 0.015 at week 10, 12, and 14, respectively.*	
T21 miscarriage (p)		0.36, 0.3, 0.25 at week 10, 12, and 14, respectively.	

AML: Algemeen Medisch Laboratorium bvba; *CVS: chorionic villus sampling;* *NIHDI: National Institute for Health and Disability Insurance;* *NIPT: non-invasive prenatal test.*
*Rounded numbers extracted from a published figure.[7]

Table 2 – Input variables (costs)

Variable	Mean	Uncertainty	Source
1st trimester screening	€80.42	/	NIHDI
2nd trimester screening	€45.03	/	NIHDI
NIPT	€460	Scenario and threshold analysis	University Hospital Leuven
Invasive diagnostic test	€934.21	Min.-max: €887.71; €980.71 (uniform)	NIHDI (and expert opinion for the distribution)
Hospitalization for leakage	€3514.54	+/- 20% (uniform)	NIHDI (and expert opinion for the distribution)
Pregnancy termination	€914.39	Min.-max: €658.24; €1170.54 (uniform)	NIHDI (and expert opinion for the distribution)

NIHDI: National Institute for Health and Disability Insurance; NIPT: non-invasive prenatal test. Exchange rate May 22, 2014: €1 = £0.81.

Figure 1 – Screening strategy with NIPT as triage test

Hosp.leak.: hospitalisation for leakage; inv.: invasive; pr.rel.misc.: procedure-related miscarriage; rep.: repeat; term.: termination.

Results

Reference case

Table 3 presents the results for the three reference case scenarios. In the current screening situation without NIPT, 170 cases of T21 are diagnosed. 96 children with Down syndrome are born, of whom 41 after a false negative screening result. There are 58 iatrogenic miscarriages after T21-related invasive testing. Total short-term costs of screening are almost €15 million and the short--term average cost per T21 diagnosed is about €87,000.

Introducing NIPT as a triage test (cut-off 1:300) results in one extra case of T21 diagnosis missed after a false negative NIPT result. However, there are much less procedure-related miscarriages after T21-related invasive testing (16 versus 58). Both total short--term costs (minus €1.6 millionmio) and short--term average cost per case of T21 diagnosed are lower.

Introducing NIPT in 1st line results in more cases of T21 diagnosed (n=215 versus currently 170), very few children with Down syndrome born after a false negative screening result (n=2 versus 41 currently), a significant decrease in iatrogenic miscarriages related to T21 (n=8 versus 58 currently). However, at a price of NIPT of €460, the short--term budget increases to almost €51 million with a tripled average cost per case of T21 diagnosed of about €236,000. The extra cost per extra case of T21 diagnosed versus NIPT as a triage test is about €840,000.

Table 3 – Results

Test strategy	Current screening	NIPT 2nd line	NIPT 1st line
(Down) births, diagnosis and miscarriages			
N° of births	122543	122554	122560
N° of Down born	96	97	63
N° of Down born (false neg. screening)	41	42	2
N° of T21 detected	170	169	215
N° of proc.rel. miscarriages	76	34	26
N° of T21 proc.rel. misc.	58	16	8
Costs for testing during pregnancy			
1st & 2nd trim. screening cost	€7.252.215	€7.252.215	€89.123
NIPT cost	€0	€2.390.929	€47.969.932
Cost invasive tests	€7.086.886	€3.203.417	€2.435.450
Cost hosp.leakage & pregn.term.	€415.728	€268.375	€279.539
Total cost (Short term)	**€14.754.829**	**€13.114.935**	**€50.774.045**
Short term cost/T21 detected	**€86.944**	**€77.696**	**€236.436**
Extra cost per extra T21 detected	/	€2.738.197§	€839.936

Proc.rel.-misc.: procedure-related miscarriage; § This result is located in the 3rd quadrant, i.e. fewer cases of T21 diagnosed with a lower cost. The results with their 95% credibility intervals (CrI) are not presented but are available upon request.

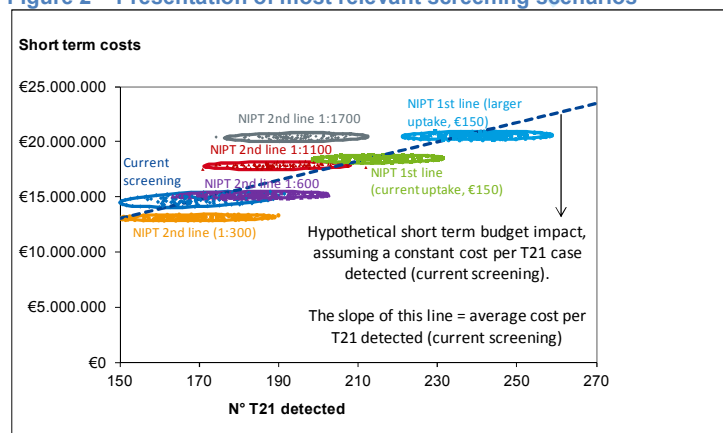### Uncertainty and scenario analyses

Figure 2 provides an overview of the most relevant scenarios, including the impact of uncertainty of all input variables. The x- and y-axis represent the number of T21 diagnoses and total short--term costs, respectively. We remark that these are not the only outcomes of importance. Other outcomes,

such as the number of procedure-related miscarriages should also be taken into consideration. Further details on all outcomes are mentioned in supplementary tables.

More patients would receive NIPT in 2nd line if the risk cut-off after 1st and 2nd trimester screening is lowered. As a result, the number of T21 detections would increase and fewer children with Down syndrome would be born after a false negative screening. The number of procedure-related miscarriages would increase only slightly each time the cut-off risk is lowered. The short-term total screening costs and average cost per T21 detected are lower compared with the current screening situation if NIPT is used as triage test with a risk cut-off of up to 1:600. However, if the risk-cut off is lowered further the extra cost per extra T21 detected increases exponentially (Figure 2 and Table 6 in supplementary material).

The threshold analysis resulted in a price of about €152 which would keep the short-term screening cost per T21 diagnosed constant if NIPT is used in first line. This is illustrated in Figure 2. At this price and the current screening uptake of about 80%, we would do much better (more T21 detected, less children born with Down syndrome after false negative screening, and less procedure-related miscarriages). At a constant average cost of about €87,000 per case of T21 diagnosed this would lead to an increase in the short-term costs, proportional to the increased detection rate (see supplementary table). The same is shown in Figure 2 for a 90% uptake scenario.

Figure 2 – Presentation of most relevant screening scenarios

See the discussion for further explanation on the interpretation of the line presenting the 'average cost per T21 detected (current screening)'. Remark: This figure does not present other outcomes of importance, such as the number of procedure-related miscarriages.

The probabilistic sensitivity analysis showed that the most important stochastic variables in the current screening model and the model with NIPT in 2nd line are the sensitivity of current screening and the probability of having an invasive test after positive screening.

Discussion

In Belgium, almost 100,000 women participate in current screening. Introducing NIPT as a contingent test or in 1st line is expected to reduce the number of procedure-related miscarriages. In addition, the number of T21 diagnoses missed by screening will be strongly reduced when NIPT is

used in 1st line. Whereas NIPT as a contingent test at a price of €460 will lead to short-term savings of about €1.6 million, NIPT in 1st line has a high impact on budgets, unless the price of NIPT is considerably reduced.

Strengths and limitations of study

The major strength of the model is the availability of context-specific real-world information and the ability to reflect the current Belgian screening situation by calibrating the model to the number of women screened, the expected and observed number of children born with Down syndrome and the number of invasive tests performed in Belgium. This calibration asensures that the initial screening model, including a large amount of real-world Belgian data on test characteristics, probabilities and costs, reflects the current Belgian screening situation as good accurately as possible. This initial model is then used to construct the 2nd and 1st line NIPT screening situation. The expected 219 births with Down syndrome if no screening is performed is used as a control variable and checked in all models and all simulations. Full details of the models are available in supplementary material.

When NIPT is compared with the current screening system, NIPT is clearly superior in terms of sensitivity and specificity for the detection of T21 and other types of trisomy. Nevertheless, the model focuses on the detection of T21 and does not take into account the effects of screening for trisomy 13 (T13) and 18 (T18). Among the aneuploidy forms, T21 has the highest birth prevalence rate.[20] Trisomy 18 occurs less frequently and T13 is rather rare and survival of neonates with T13 or T18 beyond the first days of life is rare.[21] The fetal fraction in T21 pregnancies is significantly higher compared with T13 and T18 pregnancies, which may help explain the higher sensitivity and specificity of NIPT for detecting T21.[22] More research is needed to evaluate the use of primary NIPT to detect trisomy 13 and 18 which may lead to more invasive tests because of false positive test results. iIf the current biochemical analyses are replaced by NIPT, the detection of some other chromosomal aberrations may be missed.[23] At present, the clinical importance is unclear as a NT>3.5mm will already pick up many of these abnormalities. This is of relevance, as keeping in place the biochemical screening in parallel with NIPT would lead to a much less pronounced drop in invasive testing with a different impact on both costs and effects of the NIPT scenarios modelled.

The major weakness of the model is the inability to apply a long-term horizon and translate outcomes to incremental cost-effectiveness ratios expressing results in euros per (quality-adjusted) life-year gained. Two studies incorporate a lifetime cost of Down syndrome from a societal perspective of $940,000[24] and $677,000,[25] respectively. A lifetime cost of Down syndrome of $900,000 is also mentioned by Cuckle et al.[26] This amount is extrapolated from a 1992 average lifetime societal costs for an individual with Down syndrome of $451,000.[27] The largest part (64%) was due to indirect costs (productivity losses) which were calculated with the human capital approach. However, in contrast to the friction cost approach, this over-estimates the total incremental cost for society. The friction-cost method, which is recommended by the Belgian guidelines for economic evaluations,[3] is based on the idea that organizations need a certain time span (the friction period) to restore the initial production level after an employee becomes absent from work. The amount of production lost to society will be much lower than the above stated numbers and depends on the length of this friction period.

Furthermore, quality of life is of major importance. One study included maternal QALYs in their analysis.[24] The QoL data used in this study were based on studies of Kuppermann et al.[28-30] in women

seeking genetic counselling and being less than 20 weeks pregnant. Their preferences, based on a hypothetical situation, might be very different from parents having a child with Down syndrome. Both the impact on life years (as a result of procedure-related or induced miscarriage) and QoL (e.g. on parents during testing, people with/without Down syndrome and their parents) are not clear enough to make proper calculations with a long-term horizon. Furthermore, as stated by Petrou,[31] "*the matter is complicated further when one considers the positive utility effects that might accrue from a future 'replacement' child. The important point to note, however, is that an objective economic evaluation that measures and values the resource savings that follow the abortion of the affected foetus or unborn child requires a commensurate measurement and valuation of averted benefits. Furthermore, this remains the case whenever averted costs are incorporated into the evaluation, since the foetus or unborn child is necessarily ascribed a future human status that, by any measure, will have positive value and utility.*" There are also other relevant costs outside the health care system. "*When the resource use implications for other sectors of society are considered the issue becomes more complicated: for example, the avoided excess costs associated with educational and institutional care, would need to be considered, as well as the costs of voluntary services and care incurred by the family.*"[32] Gathering the necessary information on all these incremental elements could be the subject of future research.

In an ideal situation, all of these incremental elements would be taken into account. However, a translation into (QA)LYs gained was not performed because, within the time frame of this study, not enough reliable data could be gathered to work this out. This does not mean that we consider longer term costs and effects unimportant. On the contrary, we present the impact on various outcomes such as T21 detection, procedure-related pregnancy loss and total number of Down births whether or not after a false negative screening test in a transparent way in order to inform our policy makers. Furthermore, if all harms (procedure-related pregnancy loss and Down birth after a false-negative screening result) are reduced and the cost per diagnosis stays the same, then it becomes difficult to oppose ~~to~~ the introduction and reimbursement of this new technology.

Comparison with other studies

A systematic review of full economic evaluations on the cost-effectiveness of NIPT was performed in December 2013 by searching the websites of HTA institutes and the following databases: CRD HTA, CRD NHS EED, OVID Medline and Embase. Details on the search strategy and selection process are available elsewhere.[9] Seven full economic evaluations were retained.[24-26] [33-36] All studies were published recently (2011-2013). Five were performed in the US, one in Australia[34] and one in the UK.[26] An additional economic evaluation from Ontario, Canada, was published during the writing of this article.[19]

The comparator is different across the identified studies and results are as follows:

- *Contingent screening with NIPT versus current practice*: Contingent screening is more efficient than current standard of care, providing benefits at a lower cost.[25] [33] In one of these studies, cost savings were obtained by including a cost for Down syndrome.[25] The only study without any explicit conflict of interest concludes that the introduction of NIPT for screening of high-risk pregnancies would result in better outcomes (additional T21 detected, reduced invasive testing and thus less procedure-related foetal losses), while costs would increase ~~with~~ by about 10%, which will need further policy planning.[34]

- *Contingent screening with NIPT versus universal NIPT screening*: Contingent screening is more efficient than universal screening.[26][36] The cost for contingent screening is substantially lower than with universal screening.[36] Offering NIPT to all women would only become affordable if the NIPT costs fall substantially.[26]
- *Contingent screening with NIPT versus NIPT as a diagnostic tool*: Contingent screening with NIPT is more efficient than applying NIPT as a diagnostic tool.[24]

Results of the previous studies are unfortunately not easily transferable to the Belgian context for several reasons. The populations described in the economic evaluations differ. Some model the general population of pregnant women[26][36] while the other studies only include populations at high-risk for T21. Related to this, the interventions and comparators used in the models differ. Not all studies consider NIPT in both first and second line. Only two studies include universal NIPT screening,[26][36] of which one does not include the current situation.[36] Furthermore, the values for several input variables are often not representative for the Belgian situation. For example, the sensitivity of first trimester combined screening (85%) in the study of Song et al.[25], is much higher than in the real-world Belgian population. The focus of the economic evaluation lies in the first place on the number of T21 detected. However, when comparing the estimated number of children born with Down syndrome, one should be cautious about differences in e.g. pregnancy termination which is reported to be~~ly~~ lower in e.g. the US ~~and Canada~~ compared with ~~other regions~~Europe.[37] As previously mentioned, inclusion of long-term costs and quality of life data should also be supported by better data.

The price of NIPT

The price of NIPT varies widely across the economic evaluations published in 2012 or 2013: $1200 (€880, £713),[33] $795 (€583, £472),[25] AU$743 (€479, £388),[34] and a price in the range of $500-$2000 (€367-€1466, £297-£1187).[26] The costs to perform this test are decreasing. In Belgium, the official price of the ~~u~~University ~~h~~Hospital in Leuven is €460 (£373). Sequenom has announced a low cost NIPT of $250 to $300 (€183-€220, £149-£178), to be available by the end of 2014.[38] These changes in prices, together with test accuracy, should be followed in order to take appropriate policy decisions.

Pressure for referral to NIPT

Most triage scenarios published as well as our model start from the combined ultrasound and biochemical screening. If reimbursement can be restricted to the 5% of the screened population using the 1:300 cut-off, this may actually lead to a reduction in overall harms and savings for the health care budget, even at a cost per NIPT of €460. However, in this case, there will be pressure both from physicians and patients, to further lower the threshold for referral to NIPT, officially or informally. Indeed, in the absence of rigid quality assessment, the ultrasound part of the current screening remains strongly operator (and machine) dependent. This may lead to an increase ~~of~~ in the number of women considered at risk after the current screening and thus eligible for NIPT reimbursement.

Conditions for a successful introduction of NIPT

Providing correct information and counselling and respect for the decision taken by the women or parents remains a cornerstone of any screening process.

As mentioned above the NIPT test does not provide a result in a fraction of women tested. If primary NIPT is offered at gestational week 10 the proportion of 'no result' after a repeat NIPT may be 4% instead of 2%. If most of these women would opt directly for invasive testing instead of falling back to the current screening tests as we assumed, the reduction in harms related to the invasive procedure might not be realisized. It is therefore crucial to monitor the performance of the real-life implementation of NIPT not only for sensitivity and specificity, but also for the proportion of 'no results' and the uptake of invasive testing after a 'no result' answer for NIPT in first-line.

AuthorsSeveral experts have expressed their fear that the quality of NT will decline once NIPT is broadly introduced. The ultrasound should remain a key component of the prenatal screening process also after the introduction of NIPT in second or first line. Women with a foetal NT>3.5 mm (the 99th percentile) are directly (without use of biochemistry information) offered genetic counselling, diagnostic invasive testing and follow-up in keeping with international guidelines.[19] In such cases, there is a greater than 30% risk of chromosomal abnormalities, including but not limited to T21,[17] and other abnormalities such as heart defects.[39 40]

It has repeatedly been recommended that NT based risk assessment should only be implemented in centres with appropriately trained and accredited sonographers using high-quality equipment. Results should be subject to regular audit by an external agency.[17 40] Such requirements are still to be implemented in Belgium. Also the calibration of the ultrasound machines seems to be a problem.[41] For example, an NT of 3.5mm is reported as 3.2mm on one machine and as 3.8mm on another instrument. This finding illustrates the clear need for further standardization of the NT assessment. We believe that improving the quality of the ultrasound NT assessment in Belgium could increase the overall sensitivity of the screening, e.g. from 72.5% to 77.5% at 95% specificity. This improvement has been modelled separately and confirms that any improvement of the current screening sensitivity is mainly of importance when NIPT is used in second line, reducing the number of T21 cases missed because of a false negative result. It could also help in the acceptance of the current screening as alternative test in cases where NIPT does not provide a result in first line screening. Amniocentesis and CVS carry a 1 to 2% risk of membrane rupture, a 0.3% risk of sustained oligohydramnios,[13] and a 1% risk of induced miscarriage, which may be higher after CVS as compared with amniocentesis.[14 42] It has been suggested that 100 to 400 CVSs are needed before the learning curve reaches a plateau.[42] The risk may thus be lower in the hands of experienced operators and higher in low–volume, less experienced centres. Currently, no required minimum volumes have been defined in Belgium and invasive testing is still performed in many small centres. Therefore we applied a 1% risk of procedure-related miscarriage after CVS or amniocentesis.

Conclusions and policy implications

In comparison with the current prenatal screening for trisomy 21, the appropriate use of NIPT in either first or second line clearly improves the benefit-risk ratio. Based on the availability of data, it was not possible to reliably calculate cost per (QA)LY gained. From an economic point of view, assuming that we accept the current screening situation, we recommend our National Health Insurer to cover the cost of NIPT if the introduction of NIPT does not increase the screening cost per case of trisomy 21 detected. If offered at the current price of €460, NIPT can be introduced as a triage test, even if the screening risk cut-off is lowered from 1:300 to 1:600, corresponding to about 9% positive screen results eligible for NIPT reimbursement. Attention should be paid to further increase the quality of current screening with NT. As the number of invasive diagnostic tests will likely decrease,

procedures should be centralizsed. In terms of benefits and harms, the use of NIPT in first line is preferred over its use in second line. However, the cost of NIPT should be lowered to about €150 in order not to increase the screening cost per case of trisomy 21 detected. In Belgium, at this (future) price level, NIPT should be offered to and reimbursed for all pregnant women.

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Data sharing statement: No additional data available.

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Supplementary material

Modelling of NIPT

Figure 3 presents an overview of the current screening strategy in Belgium. In Figure 4, the current first trimester biochemistry screening and second trimester screening is replaced by NIPT at week 12.

In a separate supplementary file, we present and explain the three models in detail (current screening, NIPT 2nd line and NIPT 1st line) with inclusion of the number of pregnant women and T21 pregnancies at different moments in the model.

Figure 3 – Current screening strategy

Hosp.leak.: hospitalisation for leakage; inv.: invasive; pr.rel.misc.: procedure-related miscarriage; term.: termination.

Figure 4 – Screening strategy with NIPT as first-line test

Hosp.leak.: hospitalisation for leakage; inv.: invasive; pr.rel.misc.: procedure-related miscarriage; rep.: repeat; term.: termination.

Supplementary material

In this supplementary file we transparently present the three screening models: current screening, NIPT 2nd line, and NIPT 1st line. The figures of the models are copies from the original excel file, including exact numbers. These numbers represent (singleton) pregnancies and the number of T21 foetuses is added between brackets. All transitions are mentioned on the figures and explained with a short reference to the full text of the report.[9] Small differences in numbers (maximum 1 unit) might be possible due to the presentation of rounded numbers. In the original calculations, full details with non-rounded numbers were taken into account.

Current screening:

Part 1:

- **1** : 131567 pregnant women at week 10 including 350 T21 foetuses (part 2.1.3.4 and Table 9).

- **2** : Exclusion of 1.8% twin pregnancies (part 2.1.3.3 and Table 9). 129199 singleton pregnancies and 2368 twin pregnancies.

- **3** : Impact of miscarriage between week 10 and 40 (part 2.1.3.4 and Table 9). 2368 x (1-0.05) = 2250, 8 x (1-0.36) = 5.

- **4a** → **4e** : Impact of miscarriage between week 10 and 15 (part 2.1.3.4 and Table 9).

- **5a** , **5b** , **5c** : 1st and 2nd trimester screenings (part 2.1.6.1 and Table 12): number of tests, cost per activity, and % of screening uptake. E.g. 5a) 26 056/129 199 = 20.17%.

- **6a** , **6b** , **6c** : For simplicity, numbers are recalculated to week 14 and we assume that further steps are taken at week 14 (although in reality this might be between week 11 and 20). This has no meaningful impact on results since afterwards spontaneous pregnancy termination is modelled in one step between week 14 and 40.

- **6d** : The remaining pregnant women that did not participate in screening (124 608 – 21 560 – 51 583 – 25 130 = 26 335).

- **7a** , **7b** : Total number of singleton pregnant women (not) participating in screening. Number of T21 fetusses (292 in total) is mentioned between brackets.

- **8a** , **8b** : 398 pregnant women with an ultrasound detected NT>3.5mm are referred directly for invasive testing. They are divided proportionally among the screening (n=314) and no-screening (n=84) participants (see 2.1.6.3). It was assumed that women opting for an invasive test based on NT had an increased prevalence of a T21 pregnancy of 1:10.

Part 2:

- (9a), (9b): Exclusion of the high-risk pregnancies (NT>3.5mm): 26 335 – 84 = 26 251; 98 273 – 314 = 97 959.

- (10), (10): Results of the current screening. E.g. True negatives: (97 959 – 199) x specificity of 95.0343% = 92 906; True positives: 199 x sensitivity of 72.5352% = 144 (part 2.1.6.1).

- (11), (11): After a positive screening test result, we assume 87.5% of women chooses to have an invasive diagnostic test (part 2.1.6.3). Thus (4855+144) x 87.5% = 4374.

- (12): In Belgium, there was a total of 7586 of invasive tests (part 2.1.6.3). This leaves us with 3212 (7586 – 4374) invasive tests. We already identified 398 (314+84) pregnant women with an ultrasound detected NT>3.5mm. We assume another 1000 invasive tests for T21 detection are performed in pregnant women (often at low risk) who wish to have more certainty than can be provided with the current screening, and/or are referred based on age over 35 (despite existing guidelines). The remaining 1814 invasive tests are performed for non-T21 indications, including structural anomalies detected with ultrasound not related to T21 detection. The 1000 and 84 invasive tests are specifically for T21 and were not counted before and represent another 0.87% of the pregnant population. This slightly increase the overall uptake (of any type of) testing for Down from 78.87 to 79.74%.

- (13), (13): After CVS or amniocentesis, an incremental procedure related foetal loss of on average 1% was assumed in our model (e.g. 4374 x 1% = 44). We also included a 1% risk of hospitalizsation for one week for leakage. The costs for such a stay in an acute hospital in Belgium are €3515 (part 2.1.6.3).

- (14): One of the outcomes in our model is the number of procedure related miscarriages and the number of such miscarriages related to T21 detection. The latter excludes the miscarriages related to the 1814 invasive tests performed for non-T21 indications.

- (15): In the 'no screening uptake' group, there are 23 437 singleton pregnant women (26 251 – 1000 – 1814 = 23 437).

Part 3:

- (16), (16): In our model we assume the invasive diagnostic test is 100% sensitive and 100% specific (part 2.1.6.3). E.g. (4374 – 126) – (44 – 1.3) = 4205 and 126 – 1.3 = 125.

- (17), (17): T21 pregnancy termination was induced in 95.45% (part 2.1.6.4). E.g. 125 x 95.5% = 119

- (18) → (18): Spontaneous miscarriage is taken into account (part 2.1.6.5, 2.1.3.4 and Table 9). E.g. 18a) (125 – 119) x 0.25 = 1.4; 4205 x 0.0144 + 1.4 = 62; 18c) 48 x 0.25 = 12; (23 437 – 48) x 0.0144 + 12 = 350.

- **19** → **19** : The total number of singleton births at week 40 with the number of Down births between brackets. E.g. 19a) (4205 + 125) − (119 + 62) = 4149; 125 − (119 + 1.4) = 4.3; 19c) 23 437 − 350 = 23 087; 48 − 12 = 35.7.

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8   Part 1 (current screening)
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women who are 10 weeks pregnant

1 131567 (350)   1,80%

5a 26056 €80,42 20,17%

w10 103143   1st trimester screening

women who are 10 weeks pregnant (singletons)

2

week 10 twin pregnancies

129199 (342)   2368 (8)

w11 101540   25651

women who are 11 weeks pregnant (singletons)

4a 127191 (327)   2331 (7)

5b

w12 48386   1st trimester screening 52112 25388

women who are 12 weeks pregnant (singletons)

€80,42 41,40%

4b 125886 (313)   2307 (7)

w13 48139   51846 25258

women who are 13 weeks pregnant (singletons)

6d   **6c**   **6b**   **6a**   **4c** 125244 (300)   2296 (7)

w14 26335   21560   51583   25130

women who are 14 weeks pregnant (singletons)

4d 124608 (292)   2284 (7)

5c 21451   51323   25003   2nd trimester screening

women who are 15 weeks pregnant (singletons)

€45,03 17,30%

week 15 twin pregnancies

4e 123979 (284)   2273 (6)

No screening uptake (w14)   Screening uptake (w14)   week 40 N° of twin births

high-risk   total   high-risk   total

8b 84 (8)   26335 (62) **7b**   **8a** 314 (31)   98273 (230) **7a**   **3** 2250 (5)

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Part 2 (current screening)

non-high risk
26251 **9b**
(53)

12 0,87%
non-high-risk 1000 (2,0)
non-high-risk 1814 (3,7)
high-risk 84 (8,4)

high-risk
314
(31,4)

non-high risk
97959 **9a**
(199)

Negative
test result

TN 92906 **10a**
FN (55)

Positive
test result

TP (144) **10b**
FP 4855

€934,21 Invasive test

3212 **12**
(45,5)

No invasive test

625 **11b**
(18,0)

€934,21 Invasive test

4374 **11a**
(126)

No invasive test

23437 **15**
(48)

Hospitalisation
for leakage €3.515

32 **13b**
(0,5)

Proc. rel.
miscarriage

32
(0,5)

T21 detection
related

14 **14**
(0,4)

Hospitalisation
for leakage €3.515

44 **13a**
(1,3)

Proc. rel.
miscarriage

44
(1,3)

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8   Part 3 (current screening)
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TP (Down) (45)   16b   TN 3135

€914   Pregnancy termination   17b   43 (43)

Spontaneous Miscarriage   350 (12)   18c

Spontaneous Miscarriage   18b   46 (0,5)

N° of births (with Down)   19c   23087 (35,7)

N° of births (with Down)   19b   3091 (1,5)

1356 (14)   Spontaneous Miscarriage   18d   13 (4,5)   18e

N° of births (with Down)   19d   91604 (41,0)

N° of births (with Down)   19e   612 (13,5)

TP (Down) (125)   16a   TN 4205

€914   Pregnancy termination   17a   119 (119)

Spontaneous Miscarriage   18a   62 (1,4)

N° of births (with Down)   19a   4149 (4,3)

NIPT 2nd line:

Part 1:

- ⬡1 → ⬡8b : See current screening

Part 2:

- All blue hexagons: See current screening
- ⬡11 : NIPT is offered to 4999 (4855+144) women at increased risk after current screening (part 2.1.4.2). We assume the first NIPT is repeated in 4% of cases. We assume the second NIPT test is performed about one week later and therefore also take into account the number of miscarriage during 1 week (4999 x 4% x (1 − (0.015 − 0.01)) = 199). Each NIPT test costs €460 (part 2.1.6.2).
- ⬡11 , ⬡11 , ⬡11 : We assume that after repeat testing there is no result in 2% of cases: 11b) 4999 x 2% = 100; 144 x 2% = 3. For the remaining 98% the results of NIPT screening are calculated: E.g. True negatives: (4855 x specificity of 99.84%) x (98%) = 4750; True positives: (144 x sensitivity of 99.30%) x (98%) = 140 (part 2.1.6.2).
- ⬡12 , ⬡12 : After a positive NIPT screening test result or no NIPT result (but previously a positive test result after current screening), we assume 87.5% of women chooses to have an invasive diagnostic test (part 2.1.6.3). Thus (100 + 140 + 8) x 87.5% = 217.
- ⬡13 : Same reasoning as for ⬡13 (1% hospitali~z~~s~ations for leakage and 1% procedure related miscarriages) but with other underlying numbers as mentioned on the figure.

Part 3:

- All blue hexagons: See current screening
- ⬡16 → ⬡19 : ~s~Same reasoning as for ⬡16 → ⬡19 but with other underlying numbers as mentioned on the figure.

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Part 2 (NIPT 2nd line)

non-high risk
26251
(53)   **9b**

non-high risk
97959
(199)   **9a**

Negative
test result

TN   92906   **10a**
FN   (55)

Positive
test result

TP   (144)   **10b**
FP   4855

11   repeat

€460,00   NIPT
(1st and repeat)   199

12   0,87%
non-high-risk   1000   (2,0)
non-high-risk   1814   (3,7)
high-risk   84   (8,4)

high-risk
314
(31,4)

Negative
test result

TN   4750   **11a**
FN   (1,0)

No
test result

100   **11b**
(3)

Positive
test result

TP   (140)   **11c**
FP   8

€934,21   Invasive test

3212
(45,5)   **12**

No invasive test

23437
15   (48)

No invasive test

31   **12b**
(17,9)

€934,21   Invasive test

217   **12a**
(125)

Hospitalisation
for leakage

32
(0,5)   **13b**

€3.515

Hospitalisation
for leakage

2
(1,3)   **13a**

€3.515

Proc. rel.
Miscarriage

32
(0,5)

T21 detection
related

14
(0,4)   **14**

Proc. rel.
Miscarriage

2
(1,3)

Part 3 (NIPT 2nd line)

| TP (Down) | 16b | TN |
| (45,1) | | 3135 |

€914 | Pregnancy termination
17b | 43,0 (43,0)

Spontaneous Miscarriage
18b | 46 (0,5)

Spontaneous Miscarriage
350 (11,9) | 18c

N° of births (with Down)
19c | 23087 (35,7)

N° of births (with Down)
19b | 3091 (1,5)

No further tests
11a + 12b | 4782 (18,9)

1356 (14) | Spontaneous Miscarriage | 74 (4,7)
18d

N° of births (with Down)
19d | 91604 (41,0)

N° of births (with Down)
19e | 4677 (14,2)

| TP (Down) | 16a | TN |
| (124) | | 91 |

€914 | Pregnancy termination
17a | 118 (118)

Spontaneous Miscarriage
18a | 3 (1,4)

N° of births (with Down)
19a | 94 (4,2)

NIPT 1st line:

Part 1:

- All blue hexagons: See current screening

- **[5a]**, **[5b]**, **[5c]** : The current first and second trimester screening is replaced by NIPT and we assume the NIPT is performed at week 12 (part 2.1.4.3). Taking into account the number of spontaneous miscarriages, recalculating 98,-273 singleton pregnant women from week 14 to 12 results in 99,-281 pregnant women. Furthermore, we assume that the 1000 women who are directly referred to invasive testing based on age (despite existing guidelines) or the wish to have more certainty than can be provided with the current testing, will now opt to have a NIPT test. Recalculating from week 14 to 12, this results in 1010 extra NIPT tests.

- **[6]** : One week later, 3991 repeat tests are performed (98,-774 + 1005) x 4% = 3991.

Part 2:

- All blue hexagons: See current screening.

- **[5]** : see **[5a]** in part 1.

- **[9a]** : The 314 pregnant women with an ultrasound detected NT>3.5mm continue to be referred directly for invasive testing (part 2.1.4.3). The 1000 extra NIPT tests are taken into account, thus 98 273 – 314 + 1000 = 98 959.

- **[10]**, **[10]**, **[10]** : We assume that after repeat testing there is no result in 2% of cases: 10b) 98 959 x 2% = 1979; 201 x 2% = 4. For the remaining 98% the results of NIPT screening are calculated: E.g. True negatives: ((98 959 – 201) x specificity of 99.84%) x (98%) = 96 628; True positives: (201 x sensitivity of 99.30%) x (98%) = 196 (part 2.1.6.2).

- **[11]** : In case no NIPT result is obtained after a repeat NIPT the current screening strategy is applied (part 2.1.4.3).

- **[11]**, **[11]** : Results of the current screening. E.g. True negatives: (1979 – 4) x specificity of 95.0343% = 1877; True positives: 4 x sensitivity of 72.5352% = 2.9 (part 2.1.6.1).

- **[12]**, **[12]** : After a positive NIPT screening test result or a positive current screening test result (after a NIPT no result), we assume 87.5% of women chooses to have an invasive diagnostic test (part 2.1.6.3). Thus (196 + 155 + 2.9 + 98) x 87.5% = 395.

- **[12]** : The number of invasive tests in the 'no screening uptake' arm is 2212 instead of 3212 (excluding those 1000 pregnant women: see point 5).

- **[13]** → **[14]** : sSame reasoning as for **[13]** → **[14]** but with other underlying numbers as mentioned on the figure.

Part 3:

- All blue hexagons: See current screening.

- **16** → **19f** : ~~sS~~ame reasoning as for **16** → **19** but with other underlying numbers as mentioned on the figure.

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8　　Part 1 (NIPT 1st line)
9

women who are 10 weeks pregnant

1,80%

131567
(350)

women who are 10 weeks pregnant (singletons)

week 10 twin pregnancies

129199
(342)

2368
(8)

women who are 11 weeks pregnant (singletons)

2331
(7)

5c
1010

127191
(327)

w12　26605

99281

1st NIPT

women who are 12 weeks pregnant (singletons)

2307
(7)

€460,00

125886
(313)

5b
1005

6

98774

women who are 13 weeks pregnant (singletons)

2296
(7)

3991

repeat NIPT

w13　26470

€460,00

125244
(300)

extra

5a
1000

98273

women who are 14 weeks pregnant (singletons)

2284
(7)

w14　26335

124608
(292)

women who are 15 weeks pregnant (singletons)

week 15 twin pregnancies

123979
(284)

2273
(6)

No screening uptake (w14)

Screening uptake (w14)

week 40 N° of twin births

high-risk　　total

high-risk　　total

2250
(5)

8b　84
(8)

26335
(62)　7b

8a　314
(31)

98273
(230)　7a

Part 2 (NIPT 1ˢᵗ line)

non-high risk
26251 **9b**
(53)

5

non-high-risk	1000	(2,0)
non-high-risk	1814	(3,7)
high-risk	84	(8,4)

high-risk
314
(31,4)

non-high risk
98959 **9a**
(201)

Negative test result

TN 96628 **10a**
FN (1,4)

No test result

1979 **10b**
(4)

Positive test result

TP (196) **10c**
FP 155

€934,21

Invasive test

2212 **12c**
(43,5)

€45,03

11 Current screening

No invasive test

No invasive test

€934,21

Invasive test

56 **12b**
(24,8)

395 **12a**
(174)

23437 **15**
(48)

Hospitalisation for leakage

22
(0,4) **13b**

Proc. rel. Miscarriage

22
(0,4)

€3.515

T21 detection related

4
(0,4) **14**

Negative test result

TN 1877 **11a**
FN (1,1)

Positive test result

TP (2,9) **11b**
FP 98

Hospitalisation for leakage

4
(1,7) **13a**

Proc. rel. Miscarriage

4
(1,7)

€3.515

Part 3 (NIPT 1ˢᵗ line)

TP (Down)
(43,0)

16b

TN
2147

€914

Pregnancy termination
41,1
(41,1)

17b

Spontaneous Miscarriage
32
(0,5)

18b

Spontaneous Miscarriage
350
(11,9)

18c

1396
(0,3)

Spontaneous Miscarriage

27
(0,3)

18d

18e

Spontaneous Miscarriage

6,7
(6,2)

18f

TP (Down)
(172)

16a

TN
219

€914

Pregnancy termination
164
(164)

17a

Spontaneous Miscarriage
5
(2,0)

18a

N° of births (with Down)
19c 23087
(35,7)

N° of births (with Down)
19b 2117
(1,5)

N° of births (with Down)
19d 95233
(1,0)

N° of births (with Down)
19e 1851
(0,8)

N° of births (with Down)
19f 50
(18,6)

N° of births (with Down)
19a 222
(5,9)

Supplementary material

Scenario analyses

Several scenario analyses are modelled:

- In Belgium, the overall uptake (of any type of) testing for Down is currently about 80%. If NIPT would be offered in first line, there is a possibility that the screening uptake of primary NIPT will be higher than for the current screening. A large survey in the UK suggests an uptake of primary NIPT of 88.2% (972/1103; 95%CI 86.1–90%), including respondents who would currently decline T21 screening.[43] A scenario with 90% NIPT uptake in first line is presented without changing any other input variable (see Table 4).
- In the reference case, the price of NIPT is set at €460. If NIPT would be used in 1st line, the eligible population would be much larger and scale effects could result in lower prices. Also evolution in technology will help. A threshold analysis is performed, changing the price of NIPT to keep the short-term costs per case of T21 detected at the same level as in the current screening scenario. This price was about €150. Results with this lower price are presented in Figure 2 and Table 4.
- In the reference case, a cut-off risk of 1:300 for T21 is used. Based on Belgian context-specific data, this results in a referral of about 5% of all pregnant women for definitive prenatal diagnosis using an invasive test, while the sensitivity is 72.5% (AML data). Lowering of the threshold is considered in the NIPT triage scenario. The cut-off risk with specificity closest to 95% (1:300), 90% (1:600), 85% (1:1100), 80% (1:1700) and 75% (1:2400) were selected plus the lowest reported cut-off risk of 1:3000 which has a specificity of 71%. Sensitivity and specificity are modelled with beta distributions reflecting the parameters from the AML data (see Table 5). Results are presented in Table 6.
- In Belgium, based on expert opinion, the sensitivity of the current screening could be improved by increasing the quality of the current screening, especially the quality of the nuchal translucency measure. An absolute increase of 5% in the current screening sensitivity was applied to model this, i.e. being 77.5% instead of 72.5%, without changing specificity. These results are also presented in Table 6.

Table 4 – Changing the uptake and price of NIPT

Test strategy uptake	NIPT 1st line 80%	NIPT 1st line 90%	NIPT 1st line 80%	NIPT 1st line 90%
	NIPT = €460		NIPT = €150	
(Down) births, diagnosis and miscarriages				
N° of births	122560	122542	122560	122542
N° of Down born	63	45	63	45
N° of Down born (false neg. screening)	2	2	2	2
N° of T21 detected	215	240	215	240
N° of proc.rel. miscarriages	26	27	26	27
N° of T21 proc.rel. misc.	8	8	8	8
Costs for testing during pregnancy				
1st & 2nd trim. screening cost	€89.123	€100.718	€89.123	€100.718
NIPT cost	€47.969.932	€54.191.054	€15.642.369	€17.670.996
Cost invasive tests	€2.435.614	€2.486.645	€2.435.450	€2.486.456
Cost hosp.leakage & pregn.term.	€279.698	€303.489	€279.539	€303.308
Total cost (Short term)	**€50.774.367**	**€57.081.906**	**€18.446.482**	**€20.561.478**
Short term cost/T21 detected	**€236.247**	**€237.916**	**€85.897**	**€85.769**
Extra cost per extra T21 detected	€1.038.119	€712.092	€118.870§	€106.160§

Proc.rel. misc.: procedure-related miscarriage; § The extra cost per extra case of T21 diagnosed was compared with NIPT 2nd line (i.e. the previous best alternative) but with a price of €460 for NIPT (we assume such a lower price would in first instance only be probable with high volumes of NIPT such as in 1st line).

Table 5 – sensitivity and specificity of 1st and 2nd trimester screening related to the cut-off risk

Cut-off risk	Sensitivity	Uncertainty	Specificity	Uncertainty
1:300	72.54%	Beta(103;39)	95.03%	Beta(117 144; 6121)
1:600	80.99%	Beta(115;27)	90.88%	Beta(112 018; 11 247)
1:1100	84.51%	Beta(120;22)	85.41%	Beta(105 283; 17 982)
1:1700	87.32%	Beta(124;18)	80.17%	Beta(98 817; 24 448)
1:2400	87.32%	Beta(124;18)	75.18%	Beta(92 675; 30 590)
1:3000	88.73%	Beta(126;16)	71.46%	Beta(88 087; 35 178)

Source: AML data

Table 6 – Varying the sensitivity of the current screening approach or risk cut-off if NIPT is used in 2nd line

Test strategy	Current screening	Current with 77.5% sensitivity	NIPT 2nd line (1/300)	NIPT 2nd line (1/600)	NIPT 2nd line (1/1100)	NIPT 2nd line (1/1700)	NIPT 2nd line (1/2400)	NIPT 2nd line (1/3000)
(Down) births, diagnosis and miscarriages								
N° of births	122543	122546	122554	122529	122509	122490	122476	122463
N° of Down born	96	90	97	86	82	78	78	77
N° of Down born (false neg. screening)	41	34	42	29	24	20	20	18
N° of T21 detected	170	178	169	184	190	194	194	197
N° of proc.rel. miscarriages	76	34	34	35	36	37	38	39
N° of T21 proc.rel. misc.	58	16	16	17	18	19	20	21
Costs for testing during pregnancy								
1st & 2nd trim. screening cost	€7.252.215	€7.252.215	€7.252.215	€7.252.215	€7.252.215	€7.252.215	€7.252.215	€7.252.215
NIPT cost	€0	€2.395.686	€2.390.929	€4.343.507	€6.901.721	€9.357.267	€11.687.078	€13.428.890
Cost invasive tests	€7.086.886	€3.211.490	€3.203.417	€3.288.763	€3.388.650	€3.483.651	€3.569.545	€3.636.013
Cost hosp.leakage & pregn.term.	€415.728	€276.151	€268.375	€284.228	€293.214	€301.016	€304.292	€308.923
Total cost (Short term)	**€14.754.829**	**€13.135.542**	**€13.114.935**	**€15.168.714**	**€17.835.800**	**€20.394.149**	**€22.813.130**	**€24.626.040**
Short term cost/T21 detected	**€86.944**	**€74.063**	**€77.696**	**€82.746**	**€94.188**	**€105.016**	**€117.474**	**€125.249**
Extra cost per extra T21 detected	/	/	/§§	€142.110	€442.346	€531.269	/§§§	€1.750.512

Proc.rel. misc.: procedure-related miscarriage; § This is calculated in a deterministic way since the simulations fall into different quadrants making the average of all simulations unreliable. §§ This is the initial comparator, thus no extra cost per extra T21 detected is calculated. §§§ Due to the same sensitivity and a lower specificity in comparison with the previous situation (based on the data of AML), this scenario is an example of extended dominance.

RESEARCH METHODS & REPORTING

Table

Table 1| **CHEERS checklist—Items to include when reporting economic evaluations of health interventions**

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	p1, line 5
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	p3, line 3-31
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	p5, line 4-33
		Present the study question and its relevance for health policy or practice decisions.	p5, line 35-45
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	p6, line 16-31
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	p6, line 35-42
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	p5, line 53-56
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	p6, line 34-37
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	p6, line 3-7
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	p6, line 4
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	p6, line 8-13
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	p7, line 3-19
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	not applicable
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	p6, line 48-50
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	p6, line 48 p10, line 18
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	p5, line 49-51
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	assumptions mentioned in relevant parts
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	p8, line 10-35
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	tables p9+p10
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	p12, line 7-52
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	see 20b

(continued)

Section/item	Item No	Recommendation	Reported on page No/line No
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	p12, line 54 - p13, line 50
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	not applicable
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	p13, line 54 - p17, line 35
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	p2, line 10-13
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	p2, line 15

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist